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Insight

2018 | Number 1 (digital)

ISSN 2057-4312 (print)
ISSN 2057-3286 (online)

8th Annual European Meeting on the Management of Acromegaly

Milan, Italy

Featuring summaries of presentations from:

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European Society of Endocrinology

Welcome to the 8th Annual European Meeting on the Management of Acromegaly

Milan, Italy, 8 -10 February 2018

On behalf of the Scientific Planning Committee of the eighth annual European meeting on the management of acromegaly, it gives me great pleasure to provide European Society of Endocrinology members and the wider international community with a conference report from this event.

With Italy's strong endocrine history, it was fitting for Andrea Giustina to offer his welcome on behalf of the host country to more than 200 delegates from over 20 countries to Milan. We are indebted to many individuals who helped make this event a success again, including our presenters providing country perspectives for Denmark, Australia and Japan as well as those providing multidisciplinary case studies, summaries of which are available online only. Thanks also go to Wouter de Herder for moderating our first interactive knowledge assessment "What do you know about endocrinology?" To test yourself, please turn to page 16 before checking your answers on the inside back cover.

We would like to thank Dr Rachel Arthur for her help in independently writing this conference update, and to ESE for project managing its publication and distribution. We also thank Pfizer for their continuing support of this educational event and the distribution of this meeting report.

Our final thanks go to all faculty speakers, chairs, break-out session moderators and our delegates who actively participated and engaged with the exciting scientific programme. We hope you find the meeting report as stimulating, educational and thought provoking as they did to help advance the clinical practice and management of acromegaly.

Dr Christian Strasburger, MD
For the Scientific Planning Committee.

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Insight

This conference report has been commissioned and published independently by the European Society of Endocrinology for the continuing education of ESE members and other health care professionals. The views expressed by the contributors are not necessarily those of ESE. This content focus around Pituitary and Neuroendocrinology reflects an evolving strategic approach to provide Society activity and services organised around eight specialised areas. To learn more about the benefits of ESE membership from just € 10 per year, please visit **www.ese-hormones.org.** Project delivery on behalf of ESE: **Editorial review:** Wouter de Herder and Helen Gregson. **Independent Medical Writer:** Dr Rachel Arthur MB BS. **Membership & Fulfillment:** Andrea Davis & Mail Handling International. **Project Management:** Versatility Consultants. **Design and production:** Qube Design Associates.

Endocrinology FIRST A Pfizer Programme

Pfizer Ltd. has initiated and funded the 8th Annual European Meeting on the Management of Acromegaly. The Scientific Planning Committee for this event (SPC) is comprised of specialists who provide scientific and planning oversight for the overall program and content. Its members are recognised authorities in the field of endocrinology, and they receive an honorarium from Pfizer Ltd. for this work. The highlights of this symposium reflect the scientific opinions of the individual presenters and may not necessarily reflect the opinions of Pfizer Ltd., or any of its subsidiaries, partners or employees. The publication and availability of this digital INSIGHT Conference Report on the 8th Annual European Meeting on the Management of Acromegaly have been made possible by an unrestricted grant from Pfizer Ltd. A member of the SPC has reviewed ESE INSIGHT, 2018/1 to ensure its content accurately reflects the presentations and discussions of the meeting. Pfizer have reviewed the content for medical accuracy and regulatory compliance of medical literature purposes only and otherwise has had no input into its content or publication.

Fertility and pregnancy in acromegaly

Philippe Chanson, *Paris, France*

Ovarian dysfunction is seen in 70% of women with acromegaly. Complete or partial gonadotropic insufficiency is due either to tumour mass effect with macroadenomas, or due to hyperprolactinaemia with mixed adenomas or stalk disruption. A third possible cause is a direct effect of GH/IGF-I on the hypothalamus or the pituitary, and this is suggested when the patient has ovarian dysfunction with a microadenoma only (so no increased pressure, no direct lesion of gonadotrophs and no pituitary stalk disruption) and normal prolactin levels. Similarly, GH may have a direct effect on the ovary, and this is suggested when the patient has a PCOS-like syndrome which disappears after cure of acromegaly.

A retrospective analysis was performed of 181 female patients with acromegaly at the Bicêtre Hospital.[1] Eighty-six of these patients were aged 17-44 years, and full pre- and post-treatment data were available for 55 women. Their mean age was 34 years, and only 31% of patients had normal menstrual cycles. Oligomenorrhoea was seen in 22% and amenorrhoea in 47%. Hirsutism was present in 18%, galactorrhoea in 67% and hyperprolactinaemia in 45%. Tumour mass alone was the cause of gonadal dysfunction in 6 patients, hyperprolactinaemia in 11, GH/IGF-I excess in 7, and in 14 cases the cause was inconclusive or mixed. (This was assessed by response to therapy.)

Turning to fertility in women with acromegaly, 38 of these patients conceived, 66% before the diagnosis of acromegaly and 18% afterwards. Despite active acromegaly, 12 patients had spontaneous pregnancy and delivery; four women had infertility. Thus women can conceive spontaneously even in the presence of active acromegaly. Gonadal dysfunction resolved with treatment of acromegaly in 71% of cases.

Next, pregnancy in acromegaly. The French Pituitary Group performed a retrospective multicentre study[2] of 46 women with active acromegaly of whom 39 had a macroadenoma. Most had had surgery, and a third had had radiotherapy. There were 59 pregnancies among these women; 25 women were taking DA during pregnancy and 14 SSA. In all, 64 healthy babies were delivered, with no major malformations. All but four were born at term, and macrosomia was observed in two cases. Eighteen percent of cases in the same series had gravid hypertension and 9% had gestational diabetes: both percentages were higher for uncontrolled compared to controlled acromegaly.

Still in the same series, tumoral risk during pregnancy was assessed. Four cases had visual field defects; isolated headaches occurred in 7 cases. Tumour volume as assessed by postpartum MRI was stable in 82% of cases, it increased in 11% and reduced in 8%. A literature review showed that sympomatic tumour enlargement is rare, and that very few women require surgery.

During pregnancy placental GH is produced, a GH variant which is difficult to differentiate from pituitary GH.[3] During pregnancy we see an increase in placental GH and a decrease in pituitary GH. During pregnancy in women with acromegaly, the adenoma continues to produce GH and the placenta also produces GH. IGF-I levels fall during the first and second trimesters in patients with acromegaly despite discontinuation of treatment. In the majority of cases IGF-I remains more or less stable, within the normal range, during pregnancy. After pregnancy, there is a clear increase in IGF-I levels. After delivery, acromegaly may worsen with rebound symptoms in parallel with this increase in IGF-I.

What is the effect of medical treatment for acromegaly on pregnancy outcome? Medical treatment was interrupted when patients were found to be pregnant in this series. Twenty-five pregnancies occurred during DA treatment and 14 during SSA treatment.[4] Only 4 babies were born small for gestational age. There are clearly two different attitudes—one to stop treatment at the time of diagnosis of pregnancy to avoid possible teratogenic effects of the drugs, and the other to continue treatment. In fact there are not clear differences in pregnancy outcomes and tumour risk between these[5] two strategies, though the numbers are relatively small. Octreotide crosses the placental barrier but there is minimal difference in birthweight in babies exposed to this drug during the whole pregnancy, part of the pregnancy or those not exposed to the drug at all. There is a slight decrease in the length of the baby, but the numbers are very small.

Tumour volume does not increase during breastfeeding, although some authors recommend caution if the tumour remnant is >1.2 cm. Somatostatin analogues are excreted in breast milk but there is negligible transfer of pegvisomant.

From the practical point of view, acromegaly is not a contra-indication for pregnancy. It may be difficult to initiate pregnancy: we have to normalise prolactin levels and treat the mass effect. It is preferable to normalise GH and IGF-I levels. If gonadotropic insufficiency persists then ovulation may need to be induced.

Chanson Key LearningPoints:

- **Ovarian dysfunction is common in acromegaly (70%)**
- **Symptomatic increase in tumour size is very rare**
- **GH-suppressive treatments may be safely withdrawn after conception in most patients**

Everything known, nothing new in GH?!

Richard Ross, *Sheffield, UK*

Growth hormone (GH) was discovered in the 1940s, and in the 1950s somatomedin C, as it was then called, was first described. There has not been much development in biomarkers since then although biomarkers have been developed for the detection of doping in sport.

A surrogate endpoint is a biomarker intended to substitute for a clinical endpoint; in paediatric GH deficiency the clinical efficacy endpoint is adult height. And the biochemical biomarker that we generally use for evaluation of paediatric and adult GH treatment and acromegaly treatment is IGF-I. It has good mechanistic plausibility but it does not directly represent aspects of clinical relevance. It tells you whether the patient is taking GH but it does not detect change in height velocity, body composition or quality of life. So it is not by any means a perfect biomarker, there is a need for new biomarkers.

Diagnosis of GH deficiency is quite a challenge: there is no gold standard, GH assays and cutoffs are variable, there are 20% false positive results mostly due to obesity and pubertal delay, and IGF-I has poor sensitivity as a single measurement. Murray conducted a big study with 28 centres across 14 countries, the PREDICT study, to compare gene expression in GHD with controls. The algorithm used had 96% sensitivity and 100% specificity for diagnosing GHD. It is interesting to speculate that it might be possible to make a diagnosis based on gene expression rather than measurement of GH.

Developing long-acting GH agonists is another challenge. Most of the formulations that were being tested pre-clinically or in the clinic (depot formulations, PEGylated formulations, pro-drug formulations and GH fusion technology) have dropped out. There are four formulations in play at the moment. Nutropin depot was given subcutaneously but caused injection site reactions and was withdrawn. LG LB03002 was licensed but not marketed in Europe.

Four versions of PEGylated GH have been produced. Three were withdrawn for various reasons (lipoatrophy, inability to obtain a satisfactory profile, formation of vacuoles in monkey choroid plexus) but Jintrolong GenSci is marketed in China. Phase III trials have shown that it is effective, well tolerated and non-inferior to daily rhGH. The Ascendis pro-drug ACP-001 is in phase III trials with GHD children. The Novo pro-drug with albumin was well tolerated in phase II, and phase III trials in children are ongoing. Phase III trials of MOD-4023, a fusion protein with CTP, failed to meet the primary outcome in adults but tests are ongoing in children. The Versatis fusion protein with XTEN phase III trial in children did not meet its primary endpoint of non-inferiority.

Long-acting GH is a very interesting field. These are all very different molecules. The challenge is that daily GH is very good at promoting growth in GHD children so it is difficult to show superiority, it is really about compliance and tolerance. Every molecule has its own pharmacokinetics and pharmacodynamics therefore there is the potential for different adverse effects and metabolic actions. With continuous GH secretion you may get a slightly different metabolic effect. Are both GH and IGF-I needed for optimal growth, and is there a danger in unopposed IGF-I activity? We need to be careful as we go forward with this.

Turning to acromegaly, Shlomo Melmed summarised new therapeutic agents in Nature Reviews Endocrinology 2016[6]. Trevor Howlett reviewed data from the UK in 2013: he found that both GH and IGF-I were normalised in only 55% of patients taking SSA and 36% taking DA[7]. These figures have been replicated in a number of studies around the world. Dal's paper published earlier this year found that of 84 patients only 31% had both GH and IGF-I controlled on SSA[8]. It is clear that a large proportion of patients were not optimally controlled. They recommend that we measure both IGF-I and GH nadir during the OGTT. Giustina published in 2017 a study of 37 acromegaly patients who were partial responders to SSA[9]. They were randomised to either high-frequency or high-dose lanreotide. With both regimens control improved, and IGF-I was normalised in 27% of patients. A study published in 2001 by van der Lely found that pegvisomant normalised IGF-I in 97% of patients.[10]

Turning to treatments under development, oral octreotide twice daily is able to control both IGF-I and GH. Developing antisense to mRNA for the GH receptor is another possible treatment. A phase II trial of the safety, tolerability, efficacy and PK of two subcutaneous regimens of ATL 1103 in acromegaly has shown that twice-weekly injections of 200mg lowered IGF-I, but there was a high incidence of injection site reactions.

To summarise, we are going to have a number of long-acting GH agonists available over the next few years. The various ones will have different attributes and it will be interesting to see how they work. As regards acromegaly, there is a clear need for new treatments and developments which will be effective and cost-effective without side effects.

Ross Key Learning Points:

- **New GH biomarkers are needed**
- **A number of long-acting GH agonists are likely to become available**
- **Diagnosis of GH deficiency is a challenge**

You are addicted to sugar

AJ van der Lely, *Rotterdam, The Netherlands*

There is a clear relation between sugar intake, diabetes and obesity, as shown in a recent JAMA review paper: in a meta-analysis 26 papers showed this relation, and only one of these papers was sponsored. But there were also 34 published papers that shed doubt on this relation, all of them sponsored by the sugar-producing industry.

Over the last 50 years, everybody has tried crash diets and anything else possible to reduce obesity. A new craze and a new guru appear regularly, but populations are getting fatter and fatter. What has gone wrong? First, we all believe in calories still—if you don't have insulin you cannot store anything, and that is an essential paradigm shift. The highest incidence of morbid obesity in the USA is in the Mississippi Delta; this is the same spot with the lowest female life expectancy and also with the highest intake of sugar-containing beverages. That sugar intake is responsible for the reduction in longevity and obesity.

The three main sugars that we take in every day are fructose, glucose and galactose but we always use them as the disaccharides sucrose, lactose and maltose. Now the biggest threat to all of us is the increasing intake of high fructose corn syrup, a very cheap liquid formulation from corn that is enzymatically treated so that you can artificially increase the amount of fructose in it, up to 95%.[11] It is put into anything that you can buy now, as the preferential added sugar. We as humans prefer fructose. Fructose occurs naturally in fruit, and that is relatively healthy but less so if you turn it into juice. There has been a huge increase in fructose syrup intake in the American diet in the past 30 years because the industry puts the syrup into whatever we eat. Even in countries such as Thailand where people traditionally have not eaten much sweet fruit, the pressure of the tourist industry means that more mangoes, bananas and pineapple are consumed.

Why is fructose so popular? In the hepatocyte, fructose is turned into a phosphate molecule by an enzyme called fructokinase. There is no saturation of the capacity of this enzyme no matter how many fructose molecules you consume. And so fructose metabolism is unique and very different from glucose, and fructose shows up as fat[12]. Fructose-1-phosphate cannot go upstream to turn into glycogen. So the fate of fructose is fat, there is no alternative. By contrast, glucose is turned into glucose-6-phosphate by the enzyme hexakinase. This allows the body to turn glucose into glycogen at its own pace, and this is a gradual process which depends on the state of feeding, whether the person is fasting, and so forth. Glycogen may or may not turn into fat.

Uric acid is the byproduct of metabolism of high fructose intake. We build up uric acid when we consume fructose: we share with all the large apes mutations of the uricase gene so that the activity of this gene is zero, and we are not able to convert uric acid into allantoin. The uric acid increases metabolic stress of mitochondria, which reduces the activity of aconitase 2 in the Krebs cycle. So the mitochondria stop producing ATP and start producing citrate, which acts as a substrate for TG synthesis. This can be prevented by vitamin C but again we have developed mutations which mean that we cannot produce vitamin C. Oral vitamin C supplementation is now under clinical investigation to prevent liver steatosis and the production of uric acid: vitamin C supplementation has been shown to lower serum uric acid.

Evolution holds the answers. Over time apparently the humanoids developed a perfect physiological system to turn all of the fructose that was in fruit into fat to make us sustainable for the harsh winters. In the late miocene, seasonal fruits were life-saving as there was nothing to eat at all but we are still bound to our contract with the fruit trees. And now we have started to eat tremendous amounts of fructose every year. A boy of 7 may eat his own body weight in fructose over a year. This makes us fat, which is disastrous at least to some tissues such as the liver. Unbelievably, one in three American adults has hepatic steatosis, and the number of people with cirrhosis and hepatic cell carcinoma is exploding.

The system in your brain that controls protein and fat intake is a very honest one, it knows what you need and you stop. But the system that controls sugar intake is very different, and it is the same system that smokers and other addicts use for being rewarded. And that reward system includes the craving so sugar intake is something that controls your food intake irrespective of need. Interestingly, oxytocin is apparently something that could in the future uncouple your need for anything that you might be addicted to, including carbs, but we are not that far yet.

The food industry expose us to these huge amounts of sugars. Processed foods contain vast amounts of carbs compared to the original product. You do not taste that but you eat more of it because it changes your behaviour. And this impingement of what we do is so well hidden that we do not even recognise it, nobody knows the dangers of fructose being turned so efficiently into fat, we do not have a clue about the size of the problem. That is not true of smoking anymore, but it is true of the way that the industry is promoting itself and bending reality.

I think we should really try to reduce fast sugar intake. These sugars are really bad for us. If we don't do it, then evolution will do it for us.

van der Lely Key Learning Points

- **There is a clear relation between sugar intake, diabetes and obesity**
- **We consume vast amounts of fructose, which turns inevitably to fat**
- **The craving for sugar controls intake irrespective of need**

Does gender matter when treating patients with acromegaly?

Ken Ho, *Sydney, Australia*

Acromegaly is more common in women, with M:F ratios ranging from 0.74 to 0.92 :1, and the age of acromegaly diagnosis is consistently lower in men than in women; for example, Ritvonen (2016)[13] showed that the mean age at diagnosis was 44.5 years in men and 50 years in women in Finland. An interesting feature is delay to diagnosis. Recent data showed that it takes two years longer for the diagnosis to be reached in women. [14]

Moving on to biochemistry at diagnosis, women with acromegaly present with lower IGF-I levels compared to men but very similar GH levels. For instance, Tanaka (2010) [15] reported mean IGF-I levels of 679 vs. 769 ng/ml in women vs. men (n=88). Oestrogens are likely to be the responsible for modulating this relationship.

Looking at the clinical manifestations, lean body mass is not increased in women though it is in men. However, fat mass is significantly and equally reduced in both sexes. Very interesting data report greater waist circumference in women with acromegaly when compared with age- and gender-matched individuals of equivalent BMI. Insulin resistance is much greater in women with acromegaly, and the prevalence and severity of metabolic syndrome are greater in women than men. However, the prevalence and severity of sleep apnoea are much less in women. The quality of life is more perturbed in women than in men at baseline.

Data from Ciresi (JCEM 2013)[16] listed various measures of insulin resistance among acromegaly patients. Diabetes was observed in 19.1% of men and 51.3% of women. Fasting insulin was 15.14 IU/ml in men and 21.25 IU/ml in women, and the visceral adiposity index was much higher in women (2.51 versus 1.58).

Gender is predictive of surgical outcome. For example, residual tumours were found three times more often on MRI among both premenopausal women compared with men of the same age (21.6% vs. 7.2%) and postmenopausal women compared with men of the same age (7.5% vs. 2.7%). And among factors predicting surgical failure, the odds ratio for female sex is 3.63, which is highly statistically significant.

A Finnish study followed up 330 patients over 20 years and compared them with 5,000 individuals from the general population. The SMR compared to controls is clearly higher for patients compared to controls, at 1.9; and it is much higher in women (2.5) than in men (1.4). Survival rates show progressive divergence in survival between acromegalics and controls, with a more marked divergence in women than in men.

In summary, acromegaly affects more women than men. When compared to men with acromegaly, women at diagnosis are older and have suffered longer despite seeing more physicians. They have comparable GH levels but lower IGF-I levels, are more centrally obese and have greater prevalence and severity of metabolic syndrome and diabetes mellitus. At surgery, women have larger and more invasive tumours and poorer outcome. The mortality rate in acromegaly is greater for women but there are no gender differences in causes of mortality.

To what extent does age matter?

Adrian Daly, *Liège, Belgium*

Normal GH secretion varies with age: as a general rule younger individuals have large pulses of GH secretion whereas older subjects have small GH pulses[17]. Normal IGF-I secretion also declines with age. 24-hour GH secretion declines with age in normal individuals and in patients with acromegaly. Random GH and IGF-I levels are highest at the time of diagnosis in patients aged under 18, and gradually fall as the age at diagnosis rises[18]. For a given GH level, the IGF-I level falls by 0.37 nmol/year.

There are many genetic causes of pituitary adenoma. Probably the most common genetic mutation associated with acromegaly is mutation of AIP[19]. Those patients with AIP mutations are much younger at diagnosis of acromegaly than those without the mutation (22 versus 43 years) and are younger at presentation of their first symptoms (17.5 vs. 38 years). They have larger maximum tumour diameter and higher GH and prolactin levels at diagnosis. These tumours are relatively resistant to treatment with first generation SSAs and need multiple therapies for control of acromegaly. The most severe acromegaly group is formed of patients with pituitary gigantism. These patients present at the age of 12 to 14 years[20]. More than half have invasive tumours, and long-term control is achieved in only 39%. X-LAG is a newly described infant-onset gigantism syndrome in which gene GPR101 is highly upregulated. These are the youngest patients to present with acromegaly, and again have aggressive tumours which are resistant to treatment. Some 46% of cases of gigantism have genetic causes.

What effect does age have on tumour size? According to data from the German Acromegaly Registry, among patients in their 20s and 30s, macroadenomas are more common than microadenomas; the reverse holds true for patients who are 50 or older. Age also affects response to treatment. For example, Colao (2006) showed that the percentage decrease in tumour volume and maximal tumour diameter after primary SSA treatment correlates inversely with age.

Moving to complications, in older patients acromegaly becomes part of a series of risk factors. Older acromegalic patients are more likely to have diabetes and hypertrophic cardiac disease. They may also respond differently to treatment: for example, a correlation has been shown between age and percentage reduction in the AUC for GH after a dose of octreotide.

In summary, age is highly clinically relevant:

- Age is a major determinant of severity
- Age is related to tumour size and hormonal behaviour
- Age is a key factor in pathophysiology, with particular reference to genetic causes
- Responses to treatment may vary by age

Why add a neuropsychiatrist to your multidisciplinary team?

Günter Stalla, *Munich, Germany*

There may be psychological alterations in patients with endocrine disease. In order to explore this further, NeoExNET (Excellence network for neuroendocrine tumours) has been set up with the aims of identifying relevant biomarkers and prognostic factors, and developing new therapeutic concepts for the treatment of pituitary tumours.

When brains of 44 patients with acromegaly were compared with brains from age- and gender-matched controls, white matter lesions were seen in the patients. These are a marker of neurovascular pathology. The volumes of both white matter and grey matter were larger in patients, and the cerebrospinal fluid (CSF) volume was decreased.

A study of personality was performed, comparing 70 acromegaly patients, 58 patients with non-functioning pituitary adenomas (NFPA) and 140 healthy controls[21]. Pituitary patients showed a specific personality pattern with anxiety-associated traits; impulsiveness was lower in acromegaly patients than NFPA patients.

Patients with acromegaly had poorer subjective body image compared to controls. Interestingly, body image perception in acromegaly is not associated with objective changes but with depression.

Clinical characteristics of pain were described in one study of patients with pituitary adenomas (Dimopoulou 2014)[22]. Patients with acromegaly complained of a high prevalence of body pain (73%) and headache (71%). Most patients (84%) suffered from nociceptive pain, and again pain correlated significantly with depression and poor quality of life.

Possible psychopathology is perhaps the area of greatest interest. A study performed at the Max-Planck Institute in Munich compared 81 acromegaly patients with two control cohorts. Patients with acromegaly had double the risk of affective disorders compared to patients with chronic disease, and four times the risk of affective disorders compared to healthy controls. Interestingly, mental disorders were observed many (average 9-22) years before diagnosis of acromegaly.

The best predictor of reduced quality of life (QoL) is psychopathology. This is modifiable, and is a possible target for future interventions since depression and anxiety can both be treated.[23]

What are the clinical consequences of this understanding? Neuropsychiatric evaluation needs to be included in the overall evaluation of patients with acromegaly: as a minimum, QoL should be assessed with the SF-36 or AcroQol, plus cognition should be assessed, and psychopathology sought using standardised interviews. There is a need for structured patient registries, specialised psychologists and psychiatrists with an understanding of acromegaly, and randomised controlled studies.

Symposium Key Learning Points

- **Time to diagnosis of acromegaly is longer in women**
- **Age is related to tumour size and hormonal behaviour**
- **Neuropsychiatric assessment should be part of the work-up**

The role of pituitary imaging

Jean-Francois Bonneville, *Belgium*

Pituitary MRI in acromegaly is able to show intracranial acromegalic features; the responsible somatotropinoma and the location of normal pituitary tissue; sometimes collision lesions that can complicate the diagnosis of adenoma; it can indicate cavernous sinus invasion, which is important in management of the patient; in some circumstances it can predict and demonstrate SRL efficacy; and it can visualise post-tumoral remnants.

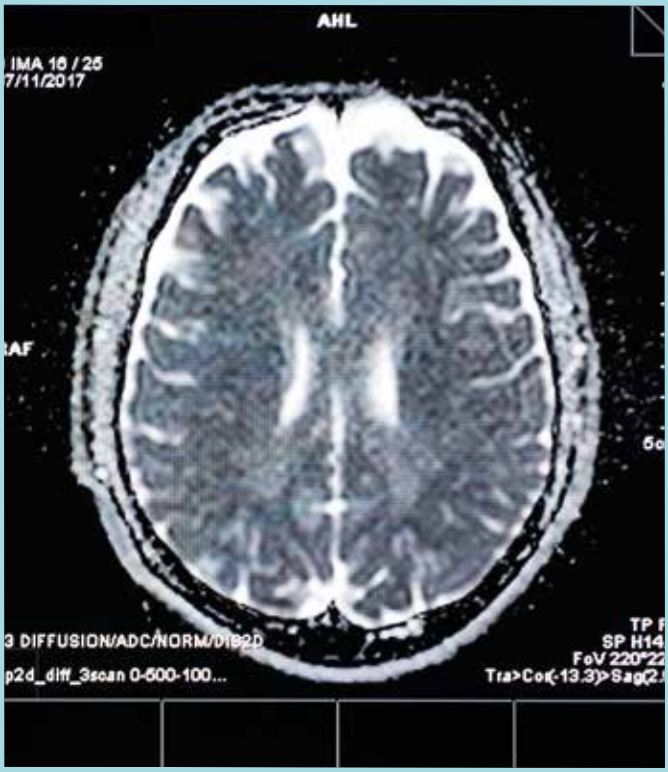
Acromegalic intracranial features seen on scans include thickening of the cranial vault; lengthening of the cerebellar tonsil; and features that are outside the sella turcica, such as enlargement of the tongue and soft palate. Other intracranial abnormalities may show up on scans. Vascular anomalies are relatively common.

Imaging demonstrates the size of the tumour—giant, large, macro, micro (30%), pico (5%), whether the tumour is necrotic, and if the patient has empty sella, which makes diagnosis difficult. Most micro and picoadenomas are located off-midline. Most macroadenomas (nearly three quarters) extend inferiorly rather than cranially, so that 17% cause visual field defects

Gadolinium contrast agents are used to enhance and improve the quality of MRI images. Very rarely there are disadvantages with these agents, such as retroperitoneal fibrosis, renal failure and anaphylaxis, and the NIH have issued a warning about these agents. T2 weighted imaging gives us everything we need, but we need high-quality images to delineate grey from white matter. T2 hypointense and T2 hyperintense adenomas (with reference to pituitary gland) are very different. T2 hypointense adenomas are smaller, have regular margins, are less invasive, and have more secretory effects (of GF). By contrast, T2 hyperintense adenomas are larger, have irregular margins, are more invasive and secrete less GF. These characteristics seem similar to those of densely granulated and sparsely granulated tumours, respectively. Isointense adenomas tend to behave like hyperintense ones.

In one series (Potorac 2015)[24], 70% of adenomas were hypointense. The hypointense adenomas were smaller, and secreted more GF. Only 11 percent of hypointense tumours invaded the cavernous sinus in this series, compared with 52% of isointense and 60% of hyperintense tumours. Hypointense tumours show a much greater response to SRL treatment, with a 38% reduction in tumour volume after six months of treatment compared to an 8% reduction in hyperintense tumours. Similarly, the reductions in GH and IGF-I are much greater for hypointense tumours than with hyperintense tumours.

In conclusion, for the management of acromegaly patients in clinical practice we support use of a simple visual assessment to distinguish T2-hypointense GH adenomas from T2-iso or hyperintense tumours. T2-hypointense GH-secreting adenomas could be good candidates for surgery. T2-hyperintense GH-secreting adenomas are likely to be poor candidates for surgery. Thus, T2 MRI can be of great help for the management of patients with acromegaly.



Potential benefits and limitations of 11C-methionine PET in acromegaly

Mark Gurnell, *Cambridge, UK*

What are the indications for consideration of 11C-methionine PET-CT co-registered with volumetric (e.g. SPGR) MRI in selected cases where standard MRI is inconclusive? Post-intervention (whether medical, surgical or RT/SRS) it might be used to differentiate post-treatment change from residual or recurrent tumour. It might also be used here to delineate foci of residual or recurrent adenoma to guide adjunctive therapeutic options such as re-do TSS or targeted RT. In de novo cases, it might be used to show the suspected site of an adenoma that is not defined on MRI.

We published the first 30 patients from the Acropet study in 2016 (Koulouri)[25]. These were 30 consecutive patients with acromegaly post primary therapy. They all had equivocal MRI scans which made it difficult to distinguish residual adenoma from post-operative changes. On PET scanning, four were PET negative and had no residual disease. Of the 26 patients with residual disease, 25 were PET positive. Of the 25 patients, 14 had PET-guided TSS, 3 had radiotherapy and 4 medical therapy. Of the 14 surgical patients, all cases were confirmed on surgery and histology. Seven patients obtained complete remission and 7 significant improvement. Normal pituitary function is spared: only 1 patient developed new pituitary deficit after the re-do TSS.

Despite these promising results, there are some cautions. Potential limitations of 11C-methionine PET in acromegaly are:

- Treatment that suppresses tumour function may result in a "negative" scan
- Low level disease may not be reliably detected on current scanners; it may be necessary to wait and scan again later
- Careful correlation with volumetric MRI is crucial as the normal pituitary gland takes up 11C-methionine. This correlation can determine whether a site of PET uptake colocalises with an anatomical or structural abnormality
- Repeat imaging should be considered prior to surgery or SRS in any patient who is treated with high-dose SSA in the intervening period

Potential indications for this technique are:

- In de novo cases when the site of adenoma is not readily identified on MRI
- To differentiate post-treatment change from residual or recurrent tumour
- To help confirm the site of residual or recurrent tumour when (further) surgery or SRS is being considered

It looks like an adenoma but it isn't: pitfalls in MRI

Hervé Tanghe, *Rotterdam, The Netherlands*

Normal height of the pituitary gland is 6mm in children; 8mm in men and postmenopausal women; 10mm in young women; and 12mm in pregnancy and postpartum. Pituitary size depends on age, gender, pregnancy, lactation, certain diseases, race and oral contraceptives.[26]

If the sella turcica is not enlarged, this suggests a rapidly growing lesion rather than a simple macroadenoma, for example Crooke's cell adenoma.

When you consider whether the lesion is a pituitary adenoma or something else, the position of the pituitary stalk is very important.

For cases with suprasellar meningioma, the questions to be asked on MRI are whether the sella is enlarged and whether the lesion can be separated from normal pituitary. It is important to make this distinction because these cases require a different operative approach, either subfrontal or lateral, rather than transsphenoidal.

A case presented was a woman 3 months postpartum with panhypopituarism and diffuse enlargement of the pituitary gland but no focal lesion. The diagnosis here was adenohypophysitis, and she was treated with prednisone. Another case of panhypopituarism was observed in a 72-year-old man. The lesion was intrasellar, infrasellar and suprasellar with very varied signal intensity and enhancement. The normal, superiorly displaced, pituitary gland could be identified. The lesion was a metastasis of non-small cell carcinoma.

Two further cases were space-occupying lesions behind the anteriorly displaced pituitary stalk. In the first case there was a CSF signal but no enhancement; in the second the signal was solid and enhancement was seen. The first case was a Rathke's cleft cyst. These are intrasellar or suprasellar mucus-containing cysts situated at the interface between adeno- and neurohypophysis. In the second, the normal, anteriorly displaced adenohypophysis could be identified. There was no fluid signal so this signified solid tumour tissue rather than a cyst. This patient had a granular cell tumour.

When should you suspect that a lesion is not an adenoma (the most common lesion) but something else?

- When the patient has panhypopituarism. This is not common with adenomas. Tumours of the neurohypophysis, pituitary stalk lesions and adenohypophysitis are more likely causes
- When the bony sella turcica is not enlarged. This is unlikely to be a macroadenoma
- When you are not able to find a pituitary gland displaced by tumour. A global lesion is more likely than a focal adenoma
- When the pituitary stalk is displaced anteriorly rather than posteriorly. This may be a lesion of the pars intermedia or neurohypophysis

Symposium Key Learning Points

- **T2 weighted MRI can be helpful for management of acromegaly patients**
- **11C-methionine PET has a place in *de novo* patients and post-intervention when MRI is inconclusive**
- **Meningiomas, cysts and metastases have to be distinguished from pituitary adenomas**

Diagnosis of anterior pituitary deficiencies in patients with acromegaly

Philippe Chanson, *Paris, France*

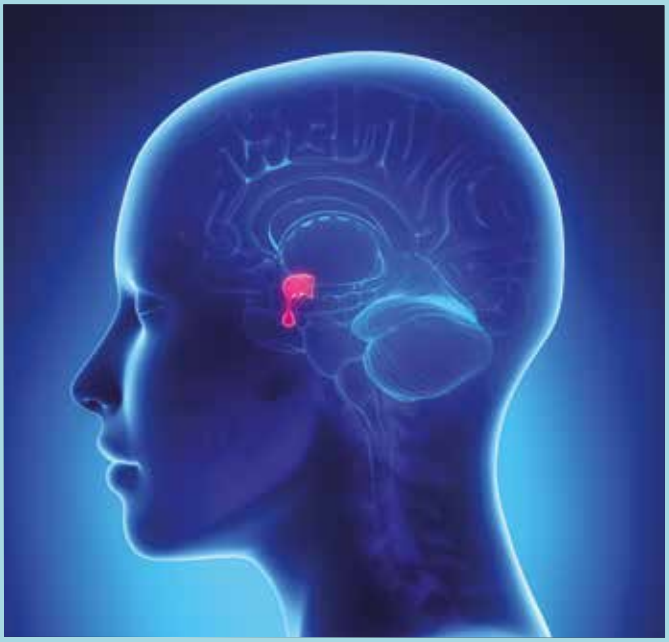
The mechanism of pituitary dysfunction in the case of macroadenomas is stalk compression or displacement although there is no correlation between the size of the tumour and the degree of hypopituarism in acromegaly. This may be also caused by increase in intrasellar pressure but this is controversial. Microadenomas can also be associated with pituitary dysfunction.

As regards measurement of anterior pituitary function, thyrotroph function can be assessed using fT4, fT3 and TSH; prolactin levels; and corticotropic function with morning cortisol, cortisol peak during ITT and ACTH stimulation test. The main way to measure gonadotropic function in women between puberty and menopause is to assess menstrual cycles. Spontaneous menstrual cycles mean normal pituitary gonadotropic function, and no hormonal measurement is needed[27]. Amenorrhoea means that gonadotropic insufficiency is likely. After menopause we measure FSH and LH. In males we measure serum total testosterone and SHBG, and also FSH and LH.

Hyperprolactinaemia in acromegaly impairs gonadotropic function per se, and also GH/IGF-I have an effect on SHBG. Raised IGF-I may be associated with decreased SHBG levels so active acromegaly may be associated with artefactually low total testosterone levels.

The prevalence of anterior pituitary deficiency at diagnosis of acromegaly is clearly lower than in other types of adenoma such as NFPA[28]. Why is this so? Somatotropinomas have mostly predominantly inferior extension (88%) compared with 38% of NFPA, particularly in males.

After surgical treatment of acromegaly a study found that there was improvement in pituitary function[29] in 30%, normalisation in 18% and no change in 50% of patients. The prevalence of pituitary deficiencies after surgery is lower in patients with acromegaly compared to those with NFPA. After irradiation about 50% of patients have some degree of hypopituarism after 5-10 years, with no significant difference between patients who receive conventional radiotherapy and stereotactic radiosurgery.



Growth hormone deficiency is diagnosed in patients with acromegaly through measurement of IGF-I and the insulin tolerance test. Sixteen studies have looked at the prevalence of GHD after surgery, with a total of 923 patients. GHD was present in 15% of patients. There are no clear data on the prevalence of GHD after radiotherapy in patients with acromegaly.

Reduced survival is seen in patients with a greater number of deficient axes; ACTH deficiency is associated with increased mortality (RR1.7); and the cause of death is cardiovascular—higher doses of either: hydrocortisone, or: glucocorticoids for replacement are associated with greater mortality.

Treatment of GH deficiency in former patients with acromegaly

Jens Otto Jørgensen, *Aarhus, Denmark*

Do we sometimes overtreat our patients with acromegaly? According to one paper, the risk of GHD is about 9% after cure of acromegaly with surgery alone; in another, severe GHD occurs in 60% of patients treated for acromegaly with surgery and follow-up radiotherapy so there seems to be some incidence of GHD in this population.

Lin (2012)[30] published an interesting paper on the effects of GHD on body composition and biomarkers of cardiovascular risk after definitive treatment for acromegaly. Patients with active acromegaly had higher total body water compared to GH sufficient (GHS) and GHD patients; they also had slightly higher trigycerides, higher 120-minute glucose and higher fasting insulin. As compared with GHS patients, those with GHD had higher waist/hip ratios, higher total fat mass, more total and visceral adipose tissue, and higher hsCRP. IGF-I levels were positively associated with fasting glucose, fasting insulin and resting energy expenditure. There was also an inverse relationship between IGF-I and hsCRP. In another paper, significantly poorer quality of life was observed in GHD patients compared with GHS patients with prior acromegaly.[31]

Another clinical study looked at GH deficiency and replacement in hypopituitary patients previously treated for acromegaly, Cushing's disease or other causes of GHD[32]. There were more females in the acromegaly group than the other aetiologies group (65% vs. 44%) and significantly more acromegalic patients had received radiation therapy (76% vs. 43%). Quality of life was also poorer in the patients with acromegaly. Perhaps surprisingly, there was no significant difference in diabetes between patients with acromegaly and those with other aetiologies of GHD. In men, the prevalence of hypertension was similar in the three groups but women with acromegaly had more hypertension compared to those with other GHD aetiologies. Stroke was more common in acromegaly patients, and a high proportion of acromegalic patients with hypertension had a stroke.

Miller 2010[33] is the only placebo-controlled study of GH replacement in patients who develop GHD after treatment of acromegaly. Its objective was to determine whether GH replacement improved body

composition, cardiovascular risk markers and quality of life. The dose of GH used was relatively high—0.58mg/day at 6 months. IGF-I level was greatly reduced at baseline in both groups; at six months, IGF-I was normalised in the group treated with GH. Body composition analysis showed that total fat mass, visceral adipose tissue and total abdominal fat were reduced in the GH group compared to the placebo group. Though hsCRP was reduced with treatment, there was no effect on other risk markers. GH replacement improved quality of life when assessed using AGHDA score, change in symptom questionnaire score and SF-36 score.

Tritos (2014)[54] performed a retrospective analysis of KIMS data to look at the effects of long-term GH replacement in adults with GHD following cure of acromegaly. Baseline demographic data showed that there were more females, more with radiation treatment and a higher prevalence of stroke in these acromegaly patients compared to the safety population of NFPA patients. There were significant differences in survival probability over the 12 years since KIMS entry between the two groups of patients: the NFPA patients actually had lower mortality than the general population.

Treatment of other deficiencies

Manel Puig Domingo, *Barcelona, Spain*

The Endocrine Society Clinical Practice Guideline on hormonal replacement in hypopituarism in adults (2016) covers many important clinical topics.[34]

Hypopituarism is associated with excess mortality, especially in women and in patients diagnosed at a young age. The SMR is similar to that found with morbid obesity. Adult hypopituarism is associated with a cluster of cardiovascular risk factors[35]. One of the causes of excess mortality in these patients is cardiac and cardiovascular disease; but prescription of protective drugs is not recommended in guidelines. More intensive treatments may reduce mortality towards that of the general population.

Factors associated with mortality in patients with hypopituarism are a previous diagnosis of acromegaly, radiotherapy, high BMI, poor control of diabetes, and cancer[36]. Desmopressin probably has little influence on susceptibility to atherosclerotic complications. Earlier diagnosis and treatment are required to address cardiovascular risk.

The "old-fashioned" treatment of glucocorticoid replacement with 30mg cortisol clearly results in worse cardiovascular risk regarding waist circumference, triglycerides and cholesterol levels[37].
All current GC replacement regimens in use may be considered supraphysiological . A modified-release hydrocortisone replacement treatment that delivers cortisol in a more physiological way is under development. Dehydroepiandrosterone (DHEA) has also been shown to improve psychological wellbeing, more in females than in males, when administered to hypopituitary patients on maintenance GH replacement.

Moving on to gonadotropic deficiency, mortality is increased in untreated patients. Sex steroid replacement brings mortality down to that seen in patients with an intact hypothalamo-pituitary-gonadal axis. In men, replacement therapy reverses most of the androgen-dependent symptoms. Aim for total testosterone level in the high normal range. In women, the aim is for age-adjusted physiological sex hormone replacement, again taking the patient's preference for route and method of administration into account in prescribing.

As regards thyroid hormone replacement[38], the guidelines recommend L-T4 in doses sufficient to achieve serum fT4 levels in the mid to upper half of the reference range, with a starting dose of 1.6 microgrammes/kg/day. The guidelines also suggest that hypothyroidism not be treated with L-T3 or other formulations of thyroid hormones. But some patients are convinced that combination treatment is better than monotherapy. This may be because of inappropriate replacement treatment; patients may need more "physiological" replacement. We see "euthyroid" yet symptomatic patients in our practice so perhaps there is an unmet need.

Finally, since interactions may occur between the replacement hormones GH, T4, cortisol, vasopressin and estradiol, it is important to reassess all the pituitary axes when a specific replacement therapy is commenced.

In conclusion, small changes in replacement may make a big improvement in symptoms. Refined and more accurate (personalised, including pharmacogenetics and new drug formulations) hormone replacement is required.

Symposium Key Learning Points

- **GHD may complicate treatment of acromegaly**
- **GH treatment of GHD in patients with cured acromegaly has potentially beneficial effects on body composition and quality of life**
- **Replacement therapy in hypopituarism should be individualised, with the aim of mimicking physiology**

Bone fractures in acromegaly

Andrea Giustina, *Milan, Italy*

Study of bone problems has not been a priority for most clinicians. A meta-analysis performed a couple of years ago (Mazziotti, 2015)[39] examined the influence of acromegaly on markers of bone metabolism. GH and IGF-I stimulate bone formation but interestingly bone resorption is much higher than bone formation in these patients. Generally speaking, osteoporosis is infrequent in acromegaly patients

The paradigm has shifted towards measurement of bone strength, which is related to both bone density and bone quality. It is difficult to diagnose and measure vertebral fractures in the community. In fact, 50% of vertebral fractures are unknown in the general population, so you need to look proactively for fractures, and the method of choice is vertebral morphometry.

DEXA machines with specific software may be useful for detecting bone morphometry. The first evidence was produced by Bonadonna in 2005, who studied 36 postmenopausal women with acromegaly.[40] The study demonstrated a clearcut increase in risk of vertebral fracture compared to controls, and with a higher risk in active acromegaly than in controlled acromegaly. Interestingly, the fractures occurred in relation to the IGF-I values and independently of BMD values. Whether patients were or were not controlled, new vertebral fractures were much more common in patients with a history of previous fracture and hypogonadism than in the general population; patients with controlled acromegaly, eugonadal status and without previous fracture had the lowest proportion of incident fractures compared to the other acromegaly patients. Male gender was not protective against fractures.

Both compressive strength and energy absorption are impaired in patients with active acromegaly compared to controls. Further studies using high-resolution cone beam CT (HR-CBCT) showed that the structure of bone is completely different in patients with acromegaly compared to controls[41]. Resistance to impact is impaired in acromegaly.

In conclusion:

- Acromegaly per se is a significant risk factor for vertebral fractures
- Bone metabolism should always be assessed in patients with acromegaly
- BMD is poorly predictive for fracture risk in acromegalic osteopathy, therefore a morphometric approach is needed
- The control of acromegaly is critical for skeletal health
- We need to assess the potential effectiveness of treatments to prevent fractures in acromegaly

Impact of acromegaly on the thyroid

Susan Webb, *Barcelona, Spain*

Dr Webb discussed some recent papers[42]. The first paper was a retrospective evaluation of 160 patients with a mean age of 49 years who were followed up for a mean of 7 years[43]. Thyroid cancer occurred in 10.6% of the patients; age and age at diagnosis of acromegaly were higher in patients with cancer. Initial IGF-I levels were also higher in patients with thyroid cancer. They concluded that patients with acromegaly should routinely be screened for cancer, especially thyroid cancer, which was 4 times commoner than breast and colorectal cancer in this cohort.

Reverter (2014)[55] conducted a cross-sectional study of 123 patients with acromegaly, with a mean age of 59 years and disease duration of 6.7 years, and they were compared with 50 controls. All patients underwent thyroid ultrasound. The main results were that 25% of acromegaly patients vs. 8% of control patients had goitre; that more acromegaly patients had nodular thyroid disease (65% vs. 29%); and that more had nodules >1 cm (53% vs. 29%). Suspicious cytology was seen in four cases but no controls. The conclusion of this study was that thyroid nodular disease and cancer are increased in acromegaly, which justifies routine ultrasound screening.

A recent paper from China (Wu, 2018)[44] found that GH, IGF-I and age are important contributors to thyroid abnormalities in patients with acromegaly. They performed ultrasound on 93 newly diagnosed patients and found abnormalities in 77%, and thyroid cancer in 3.2%. Thyroid volume was greater, and was correlated with higher GH/IGF-I values and with GH exposure. Patients who had thyroid alterations were older than those who did not.

The issue of whether acromegalic patients with papillary thyroid cancer have the BRAF mutation was investigated in a study from Korea (Kim, 2014)[56]. Thyroid cancer was found in 25% of patients, a much higher percentage than in the other studies described. Those patients who had PTC more frequently had active acromegaly. The BRAF mutation

was only found in 9% of acromegalic patients with PTC, in contrast with 63% of non-acromegalic patients with PTC.

A meta-analysis and systematic review from Poland (Wolinski, 2014)[45] showed that the odds ratio of patients with acromegaly having thyroid nodular disease was 3.6, and for thyroid cancer was 7.9.

What about thyroid dysfunction in patients with acromegaly? A review of thyroid diseases in patients with acromegaly (Dabrowska 2014)[46] found that 67% of patients are euthyroid, that 25% have hypothyroidism, and somewhere between 3% and 26% have hyperthyroidism.

Finally, Manavela (2015)[57] investigated thyroid autoimmune disorders in acromegaly, conducting a retrospective evaluation in 116 acromegaly patients of TSH, total T4, ATPO antibodies and thyroid ultrasound. They found an increase in antibodies in 25% of patients, more frequently in women, compared to 10% of controls; prevalence of goitre was 36%, again more frequent in females; and that 35% of thyroid nodules and 44% of goitres diagnosed on ultrasound were positive for antibodies.

Sodium and fluid metabolism in acromegaly

Peter Kamenicky, *Paris. France*

These patients present with excess GH and IGF-I levels, and this leads to an increase in extracellular volume[47]. Extracellular body water is increased in acromegaly patients compared to normal volunteers. From the clinical point of view this can be observed in many different ways. Dysmorphic features are due in part to sodium and water retention, and these features disappear to a certain extent after successful treatment. This is also true for cardiomyopathy, which is due in part to oedema of the ventricular wall. In the lung and upper airways, sleep apnoea is also caused by sodium and water retention which cause obstruction. Nerve infiltration in the ulnar nerve, for example, can cause paraesthesia. An increase in plasma volume can contribute to hypertension.

How does GH exert its antinatriuretic action in the kidney? Sodium reabsorption takes place in all parts of the kidney. In the loop of Henle reabsorption of sodium and chloride is mediated through the sodium-potassium-chloride co-transporter NKCC2. In the distal tubule the sodium chloride co-transporter NCC is active, and in the collecting duct the epithelial (or amiloride-sensitive) sodium channel ENaC mediates sodium reabsorption[48]. Aldosterone is the key regulator controllng sodium reabsorption.

We used a rat model of acromegaly to investigate renal function. We subjected the rats to two pharmacological challenges—furosemide, which blocks the NKCC2 channel in the loop of Henle, and amiloride, which inhibits the ENaC channel in the collecting duct. GC rats had decreased furosemide-induced natriuresis compared to controls, and increased amiloride-stimulated natriuresis compared to controls. We also found enhanced Na-K-ATPase activity in the cortical collecting ducts (CCD), showing that increased sodium reabsorption occurs in the late distal nephron under chronic GH excess. GH stimulates

sodium transport in the distal nephron via ENaC. Lower aldosterone concentrations were found in the distal part of the nephrons of GC rats. Thus, GH exerts a direct, aldosterone-independent antinatriuretic action in the kidney. Further studies in a mouse cortical collecting ducts model showed synergic action of GH and IGF-I in the CCD.

Is acromegaly associated with increased ENaC activity in humans? The AcromENaC study set out to investigate this question. It was a PROBE trial design crossing over furosemide and amiloride in 16 acromegaly patients with a mean age of 49 years[49]. Patients had standardised sodium (150mmol/day) and potassium (80mmol/day) intake for 7 days before and during investigations, and the intranasal potential was measured. Good control of acromegaly was obtained in all patients.

We used furosemide to functionally exclude the loop of Henle, and amiloride treatment to directly inhibit ENaC. Active acromegaly increases the response to amiloride, decreases the response to furosemide, and increases the intranasal amiloride-sensitive potential. The CCD are a direct target of GH. GH stimulates sodium transport via the ENaC channel, leading to water and mineral imbalance. These changes may contribute to the soft tissue swelling and volume expansion that are observed in acromegaly.

Symposium Key Learning Points

- **The structure of bone is different in patients with acromegaly**
- **Patients have a high prevalence of thyroid nodules and cancer**
- **GH stimulates sodium transport, leading to water and mineral imbalance**

Pituitary apoplexia or chiasma compression: call the surgeon or send them away?

Chair: John Wass, Oxford, UK.

PROPOSER: Dr Michael Buchfelder, *Erlangen, Germany.*

Dr Michael Buchfelder (Erlangen, Germany) proposed that in the threatening condition of pituitary apoplexy, it was better to call the surgeon. Pituitary apoplexy is the acute occurrence of haemorrhagic or non-haemorrhagic infarction of a pituitary adenoma. This is an acute event which leads to a rapid increase in intrasellar volume and pressure to which the surrounding structures cannot adapt, so they are acutely compressed[50]. This concerns the cranial nerves III, IV and VI (causing diplopia) and II (with chiasmal compression), the CSF pathways causing obstructive hydrocephalus, and pituitary tissue causing pituitary insufficiency. It is a true neurosurgical emergency.

Surgeons from Boston, Massachusetts operated on almost all their patients and the results were very good because symptoms resolved or improved in the vast majority[51]. And a Turkish study[58] of 186 blind patients showed some recovery of vision in about 60% after surgery even after a delay of some days to surgery.

Another paper[59] compared outcomes in patients treated surgically (n=15) and conservatively (n=18), and appeared to show that visual field recovery and ocular palsy recovery were better in the conservatively managed group. However, the study was biased.

Although the UK guidelines for the management of pituitary apoplexy advocate that surgery should be considered in the presence of severely reduced visual acuity, severe or deteriorating visual defects and deteriorating level of consciousness, they should urge you into surgical management, he said[51]. The lack of clarity for treatment paradigms may be related to the fact that diverse patients are often lumped into one group. To conclude:

- Pituitary apoplexy is not a homogeneous clinical entity
- Surgery offers rapid decompression of all compromised structures
- Remarkable recovery of neurological function has been documented after surgery
- There is enormous bias in the literature as to which patients were treated surgically and which treated conservatively
- A direct comparison is not yet possible
- Since data are poor, proper studies are needed

In Summary

This is a neurosurgical emergency but patients come with some delay. Why in the case of severe visual deterioration should the patient wait so long? Publications suggest that the earlier the intervention the better the chance of recovery. We are probably misled because some of the cranial nerves are pretty stable so that decompression after a few days still leads to good recovery. But this is not the case for the optic nerve, and the pituitary cannot survive under conditions of high ICP. If surgeons do not get involved for a week we do not have the chance to rescue the pituitary and preserve pituitary function.

Start of Debate

End of Debate

OPPOSER: Dr Ariel Barkan, *Michigan, USA*

The motion was opposed by Ariel Barkan (University of Michigan, USA). Pituitary tumour apoplexy can be haemorrhagic or ischaemic, and is most often seen in macroadenomas. The cause is often unknown or it can be associated with coagulation disorders, sudden hypotension, releasing factor injection or use of dopamine agonists. The classical description is a sudden thunderclap headache, visual problems (blindness, visual fields impairment, ophthalmoplegia), nausea/vomiting, shock and altered level of consciousness. In an unknown percentage, it is asymptomatic.

How urgent should pituitary surgery be? Information is exceedingly sparse. One of our residents analysed 25 patients with a reduction in visual acuity (37 eyes). Surgery within the first four days after initiation of symptoms resulted in 100% normalisation or improvement in visual acuity. After four days, only 75% of patients improved. So there is a hint that the first four days might be quite important. Similar results were reported by Rutkowski (2017)[60]; of 32 patients, 13 (41%) had surgery within 72 hours of admission, and there was improvement in 67% with normalisation in 33%. Of the 19 patients (59%) whose surgery was delayed for longer than 72 hours after admission, 84% improved and 41% normalised.

Several studies have advocated wider use of conservative therapy based on similar outcomes but these studies have all been retrospective, treatment was assigned without firm criteria, and they were biased in that patients with severe or worsening visual symptoms were sent to surgery, so we do not know the outcome for patients with moderate visual abnormalities.

What about endocrine outcomes? In all studies addressing this issue, long-term hypopituarism after pituitary tumour apoplexy was seen in 60-80% of cases irrespective of treatment approach.

Jho and colleagues from Massachusetts General observed 109 cases of pituitary tumour apoplexy and developed a 5-point grading system[52]. In all, 93% underwent surgery: vision was normal in 100% of G1-2; 82% in G3; 73% in G4 and 60% in G5. Hormone replacement was 0-23% in G1-2, and 62-68% in G3-5. This system is pretty good for categorisation and outcomes but it does not provide any management guidelines. To conclude:

- Pituitary tumour apoplexy is likely to be more common than we think
- An unknown proportion may be asymptomatic
- More than 90% of hospitalised patients undergo surgery. The timing of it may be important but this is controversial
- Patients with normal vision and normal level of consciousness may be treated conservatively, though the data to support this are extremely sparse
- Hypopituarism is equally frequent irrespective of the mode of therapy
- All published therapies are retrospective, lack sufficient numbers, and treatments are assigned based on the investigators' biases
- So maybe it would be a good idea to organise a prospective multicentre study to resolve the controversies and provide valid management recommendations

In Summary

We definitely agree that the patient with acute significant visual impairment or very high GCS needs surgery as soon as possible. People who do not have visual or neurological impairment require observation. The only thing is, how long should we observe patients who have some degree of impairment: is it worth risking the patient's vision in order to avoid a surgical procedure? Another thing that I would like to suggest is that we should measure the duration of apoplexy from the time of clinical onset.

Delegates to the meeting were invited to participate in two breakout sessions, to discuss specific questions raised by material presented in the plenary sessions and symposia. There were four discussion groups – yellow, red, blue and green – and some key points from the groups are given below.

Breakout session 1

Q1. Is the desire to have children an issue in your patients with acromegaly? If so, how do you manage this?

Yellow. Yes, it is. In mild acromegaly medical treatment can be tried first if pituitary function is normal; but in most patients consider surgery. Ovulation might need to be induced. If headaches develop during pregnancy they can be effectively treated with SSA or DA. And finally, what happens later to the babies born small for dates?

Red. If there is good biochemical control then you can stop treatment, though some believed that we should stop treatment anyway. DA are sometimes used, and if continuing with bromocriptine then the lowest possible dose should be used.

Blue. This is not a frequent problem in clinical practice because of the age range of patients with acromegaly. When it is an issue for the patient and she wants to have children, in the majority of cases the endocrinologist can manage this easily. In patients who have normal pituitary function, before potentially invasive surgery its possible impact on fertility should be discussed.

Green. If the patient becomes pregnant while on SSA, most of the group would continue treatment though it would depend on tumour size and other factors. If the patient wants to have children pre-operatively then IVF might have to be considered.

Q2. Does your approach to the diagnosis and treatment of acromegaly differ by gender?

Yellow. We thought no.

Red. There are apparently more female patients than male with acromegaly although the historical view was mainly focused on male patients. Oral contraceptives or oestrogens might be used in patients with low-activity disease.

Blue. In real life, diagnosis and procedure is the same in males and non-pregnant females. Treat the patient individually. There might As regards the epidemiology of acromegaly in Japan, the Japan Intractable Diseases Registry reported in 2016 some 21,871 patients with hypothalamic and pituitary disease; of these patients some 4,337 patients had acromegaly. The Japanese population is 127 million so the prevalence is about 4 per 100,000. This contrasts with 874 patients listed with Cushing's disease. The age distribution (the Japanese population is ageing) shows that the largest number of acromegaly patients is in the age group 60-69 years.

The Research Committee of Surveys and Research on intractable diseases has been sponsored by the Ministry of Health, Labour and Welfare since 1973. The Japanese Agency for Medical Research and Development has sponsored a taskforce to develop a guideline on hypothalamic and pituitary disease, consisting of 22 experts and supported by the Japanese Endocrine Society and the Japanese Society for Hypothalamic and Pituitary Disease.

The Toranomon Hospital, Tokyo is probably the most famous institute for surgical treatment of acromegaly in Japan. They undertook more than 4,300 pituitary surgeries between 2004 and 2017, which translates to roughly 100 surgeries a year. They have a very nice remission rate of 92% for microadenomas and 80% for macroadenomas. The division of diabetes and endocrinology at Kobe University Hospital, a representative medical institute, saw 172 acromegaly patients between 2001 and 2017. The division has about 180 in-patients a year and about 9,000 outpatients a year with endocrine disease.

There are many issues to be addressed for the management of acromegaly in Japan. The main purpose of the registry system is to support individual medical costs. It is not mandatory, and is be a difference in frequency of estrogen supplementation in hypogonadal acromegalic women.

Green. Menstrual irregularities may point to the diagnosis of acromegaly. We thought that we should be a bit more cautious about surgery in women of reproductive age, and fertility issues might have to be addressed for women and men. Guidance on doses of pegvisomant by gender would be welcome.

Q3. Do treatment goals for patients with acromegaly differ by age?

Yellow. They probably should not differ by age but in practice in elderly patients the goals do differ because we are primarily treating symptoms. We need more data.

Red. It is very important that younger patients are treated more strictly. We should be aware of family history, possible AIP mutation, tumour size (sometimes larger in young patients), and difficult-to-treat younger patients.

Blue. Treatment goals are mostly the same but treatment strategies may differ according to the age of the patient. The younger the patient, the more aggressive you should be in order to control the IGF-1 and the tumour. In very elderly patients other co-morbidities (especially diabetes and heart failure) should be taken in to account when deciding treatment options.

Green. In younger patients we try for surgical cure rather than medical control. Additional complications and co-morbidities tend to be less common in younger patients. The IGF-1 level can be difficult to interpret in adolescents and in the elderly. The group felt more cautious about use of radiotherapy in both the very young and the very old.

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There are many issues to be addressed for the management of acromegaly in Japan. The main purpose of the registry system is to support individual medical costs. It is not mandatory, and is be a difference in frequency of estrogen supplementation in hypogonadal acromegalic women.

Green. Menstrual irregularities may point to the diagnosis of acromegaly. We thought that we should be a bit more cautious about surgery in women of reproductive age, and fertility issues might have to be addressed for women and men. Guidance on doses of pegvisomant by gender would be welcome.

Q3. Do treatment goals for patients with acromegaly differ by age?

Yellow. They probably should not differ by age but in practice in elderly patients the goals do differ because we are primarily treating symptoms. We need more data.

Red. It is very important that younger patients are treated more strictly. We should be aware of family history, possible AIP mutation, tumour size (sometimes larger in young patients), and difficult-to-treat younger patients.

Blue. Treatment goals are mostly the same but treatment strategies may differ according to the age of the patient. The younger the patient, the more aggressive you should be in order to control the IGF-1 and the tumour. In very elderly patients other co-morbidities (especially diabetes and heart failure) should be taken in to account when deciding treatment options.

Green. In younger patients we try for surgical cure rather than medical control. Additional complications and co-morbidities tend to be less common in younger patients. The IGF-1 level can be difficult to interpret in adolescents and in the elderly. The group felt more cautious about use of radiotherapy in both the very young and the very old.

Q2. Should the diagnostic and therapeutic approach to central hypothyroidism differ from primary hypothyroidism?

Blue. Yes, of course it is different but GPs do not always appreciate that. Use free T4 for both diagnosis and follow-up, and try to maintain free T4 in the upper quarter of the normal range.

Green. The consensus was yes. The evaluations are very similar in some ways but the clinical context is different and of course TSH is critical in excluding primary hypothyroidism as the cause of the low T4. Tertiary care centres often delegate the management of thyroid levels in central hypothyroid patients. FreeT4 levels are often calculated rather than measured, which may cause problems.

Red. and yellow. Most of the group were guilty of undertreating secondary hypothyroidism. The main thing is to target the free T4 to the upper limit of the normal range. There were a few members who felt that using a personalised approach, adding T3 to T4 if the patient does not respond completely, may have a role.

Q3. Do bone problems in patients with acromegaly differ from patients with non-functioning pituitary adenomas?

Blue. Yes, the problems are different because of the larger size of the acromegalic bones and the larger cortical bone. You cannot use bone densitometry because it is poor in identifying osteoporosis. In clinical practice evaluation is done based on symptoms usually because there are no clear guidelines but if there are co-morbidities which would worsen bone health like diabetes or hypogonadism then try to control these co-morbidities in a strict way and consider pro-active treatment such as anti-resorptive drugs.

Green. In short, yes. There are some shared risk factors for reduced bone density and for fracture risk such as hypopituarism, and more studies are required. It would be interesting to see how we can affect the prospective course of these patients.

Red and **Yellow.** Bone densitometry is a disappointing tool because it is not sensitive and can even be misleading because values may be higher than in non-acromegalic patients. Simpler tools like taking a history and measuring height and taking spinal X-rays might be more useful in making the diagnosis and working out management strategies. In the absence of any data, consider treating these patients with the usual antiresorptive agents.

Q4. Should patients with acromegaly routinely be treated with diuretics? If so, which is the preferred substance?

Blue. No, unless they have a clear indication for diuretics.

Green. Currently diuretics are not routinely indicated for patients with acromegaly. Hypertension in acromegaly should follow the management of our other hypertensive patients, with a key role for ACE inhibitors. Controlling IGF- 1 is critical for managing hypertension and associated co-morbidities in these patients.

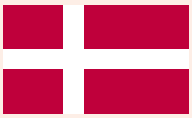
Red and **Yellow.** Not routinely but consider a sodium channel blocker such as low-dose amiloride if the patient has oedema or the BP is uncontrolled. Follow the usual hypertension guidelines, and bear in mind that you need to treat the acromegaly also and get the IGF-1 and GH level into the most appropriate range.

Q5. How do you locally organise your multidisciplinary pituitary team to manage patients with aggressive tumours?

Blue. Most centres have access to neurosurgery, neuroradiology and endocrinology, and if necessary radiotherapy, routinely. Some of us had multidisciplinary teams including these colleagues and pathologists who meet to discuss patients. Access to medical treatment with temozolomide is not always possible for the endocrinologist, and often has to be done by collaboration with the neurooncologist.

Green. Our multidisciplinary pituitary teams from various countries usually involve an endocrinologist and a neurosurgeon at the very least. Some members of our group did have an involved ophthalmologist reviewing visual field perimetry results. It should ideally include a radiation oncologist and in some cases a clinical geneticist. Patients with aggressive pituitary tumours can really benefit from having involvement of a clinical geneticist, whether because they have a germline genetic mutation or because of the possibility of somatic studies which could actually allow targeted treatment for these patients.

Red and **Yellow.** Most should have a multidisciplinary team to optimise patient care. Experienced pituitary surgeons, medical and radiation oncologists and pathologists should be involved in order to establish pituitary centres of excellence. Surgeons should be encourage to publish their success rates but the whole team should know about cure rates for micro and macroadenoma.



Country perspective: Denmark

Jens Otto Lunde Jørgensen

In Denmark there are five regions to take care of patients with endocrine diseases such as acromegaly, and our population is 5.5 million. As regards management, Denmark has universal tax-supported health care through its national health service, and medical treatment of acromegaly is provided free of charge from hospital pharmacies. The country has five endocrine units (which meet biannually to discuss guidelines and so on) and 3-4 neurosurgical units. The entire country could be described as a cohort, since a unique ID is assigned to every Danish citizen at the time of birth. It is a 10-digit number with the person's birthdate and digits that indicate his place of birth and gender. This number is used everywhere, whether the patient goes to the GP, pharmacy, hospital or social services so it is relatively easy to put together all these individual data and to construct population-based databases for medical conditions.

An excellent publication by Jakob Dal (EJE, 2016)[1] described the incidence, prevalence, complications and long-term prognosis of acromegaly in Denmark. Incident cases were identified from health registries between 1991 and 2010, and each chart was reviewed to confirm the diagnosis of acromegaly, to search for lab results and to identify treatment modality. In all, the cohort consisted of 405 patients. Of these, 80% received surgery as their primary treatment, and 35% had surgery as their only treatment. As regards medical therapy, 56% of patients received SSA as primary or secondary treatment, 17% received pegvisomant and 12% dopamine agonists. Some 17% received irradiation at some stage.

The ID number means that it has been possible to generate studies with an almost 100% capture rate for the Danish population, and to generate a reference population. Thus, the true mean age of diagnosis of our cohort is 48.3 years, the annual incidence is 3.8 per million population and the prevalence 85 per million population. The mean age at diagnosis and the incidence have remained fairly constant over the years but this prevalence is higher than previously reported.

Our data show that heart failure, acute myocardial infarction, stroke, diabetes, osteoarthritis, hypertension and sleep apnoea are more common in acromegaly patients than in the control population. Also, interestingly, even prior to the formal diagnosis of acromegaly there is an increased risk of hypertension, heart failure and diabetes in these patients. The mortality is slightly increased (HR 1.3), mainly due to cardiovascular disease; the hazard ratio is already elevated early after diagnosis and the risk is more pronounced in younger patients.

A recently published paper (Dal, EJE 2018)[2] was a randomised multicentre study targeting either GH or IGF-1 in 84 patients taking SSA treatment (these parameters are often discordant in acromegaly). The authors found that discordant values (high GH) were prevalent among these patients, especially if applying glucose-suppressed GH nadir.

Queen Margrethe II of Denmark is a known cigarette smoker. Could there be a link with epidemiology? Some colleagues think that there might be. All-cause mortality in women is declining in all western European countries with the exception of Denmark, where the decline stopped in 1978 (about 5 years after her ascension to the throne). Could the Queen be a role model and an explanation for the atypical mortality figures? The audience and readers can decide. But the quality of life in Denmark is the best in the world: in a recent survey the proportion of respondents who said that they were satisfied or very satisfied with their quality of life was 65%, significantly better than in the other 14 EU countries surveyed.

Country perspective: Australia

Ken Ho, *Sydney*

The area of Australia is about 7.7 million square kilometres compared to Europe's area of 3.5 million square kilometres. There are just four or five major centres in the whole of Australia for treating acromegaly, so clinicians face huge logistic challenges.

Australia has a publicly funded universal healthcare system called Medicare. It is partly funded by taxpayers, who pay a levy of 2% of their taxable income. The annual health expenditure is approximately $140 billion for a population of 22 million across this huge land mass. The government pays service providers and subsidises health insurance funds. There is also a private healthcare system: the more wealthy taxpayers pay a premium to health insurance companies, who also pay health service providers. Health expenditure has risen from about 40 billion dollars a year in 1986 to more than 140 billion dollars in 2013. For the year 2013 health expenditure represented about 9% of GDP. How does health expenditure in Australia compare with that of European countries? Denmark, Belgium and the Netherlands all spend roughly 10% of GDP on health, but the figure is much higher for the United States.

In Australia we have the Pharmaceutical Benefits Scheme (PBS), a nationally funded scheme that funds subsidy of medications based on cost-effectiveness. This means that not all drugs are subsidised: drugs are only subsidised after rigorous review by committee. Once approved, then a drug becomes available for subsidised access. Government expenditure on the PBS has grown from about 2 billion dollars a year in 1995 to about 7 billion in 2007. The annual cost of cabergoline is about $1,600: this is not approved by the government for the treatment of acromegaly and cannot be subsidised but endocrinologists will always try dopamine agonists first to see how the patient responds. Other drugs for acromegaly (octreotide, lanreotide, pasireotide and pegvisomant) are much more expensive but they are all subsidised; the patient only pays $40 per prescription, so patients with acromegaly in Australia do have access to the drugs that they need.

Australia does not have a national acromegaly registry, and unfortunately there is no information on the epidemiology of this disease. With a population of 22 million, the estimated prevalence is 1,500-2,000 patients and the estimated incidence 150-200 cases a year. Information on acromegaly comes from individuals or centres with an interest in the condition. A paper on trends in surgery, hospital admissions and imaging for pituitary adenomas in Australia was published earlier this year (Crowther 2018)[3]. Admissions rose from 7.1/million in 2000 to 17.2/million in 2003, and then declined again. So these are the only data on prevalence that we have, and are based on hospital admissions.

In 2008 we undertook a patient survey through the Australian Pituitary Foundation. Some 98 patients were included, and we found that the mean duration of symptoms before diagnosis was 8.2 years. The most common symptoms present at diagnosis were, in order: growth of hands/feet; changing facial features; arthritis; excess sweating; reduced energy; and headache. What about the patient journey? The patient first goes to see the general practitioner, who then refers the patient if necessary to the specialist endocrinologist, opthalmologist or neurosurgeon. In Australia, the patient cannot go directly to the specialist.

We have all the treatment options that are available in Europe—a range of pharmacotherapies, surgery and radiotherapy. The choice will depend on factors such as age, gender and co-morbidities. We are conscious of costs. As an example, if you take a patient aged 40 years with a diagnosed microadenoma and a life expectancy of 80 years, if he has surgery then the efficacy is 80% at a cost of about $25,000 but this treatment is only given once so the lifetime cost is $25,000. In contrast, treatment with SSA might be 40% effective, costs about $40,000 per year and is given for 40 years, giving a lifetime cost to the taxpayer of $1,700,000.

So, in conclusion, from the Australian perspective:

- A national healthcare system provides an excellent infrastructure for affordable management of acromegaly
- Options for treating acromegaly are available in the public and private systems
- The treatment paradigm in Australia is similar to that in the US and Europe
- The absence of a national acromegaly registry limits objective comparison of resourcing and outcome with other countries

Country perspective: acromegaly in Japan

Yutaka Takahashi, *Kobe*

As regards the epidemiology of acromegaly in Japan, the Japan Intractable Diseases Registry reported in 2016 some 21,871 patients with hypothalamic and pituitary disease; of these patients some 4,337 patients had acromegaly. The Japanese population is 127 million so the prevalence is about 4 per 100,000. This contrasts with 874 patients listed with Cushing's disease. The age distribution (the Japanese population is ageing) shows that the largest number of acromegaly patients is in the age group 60-69 years.

The Research Committee of Surveys and Research on intractable diseases has been sponsored by the Ministry of Health, Labour and Welfare since 1973. The Japanese Agency for Medical Research and Development has sponsored a taskforce to develop a guideline on hypothalamic and pituitary disease, consisting of 22 experts and supported by the Japanese Endocrine Society and the Japanese Society for Hypothalamic and Pituitary Disease.

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There are many issues to be addressed for the management of acromegaly in Japan. The main purpose of the registry system is to support individual medical costs. It is not mandatory and is designed for clinical and epidemiological study. A more comprehensive system is necesssary. As regards surgery, more than 200 hospitals perform surgery for acromegaly. The system is not centralised and the surgical skills are not standardised. Similarly, Japan has an uneven distribution of experienced endocrinologists, so that diagnosis and medical treatment are not standardised. Patients who live in the countryside may find it difficult to access medical treatment. Finally, we need a good biobank for pituitary disease.

Moving on to a description of a basic research project, Dr Takahashi discussed a genetic analysis of somatotropinomas in Japan (Matsumoto, 2016)[4]. Sixty-one consecutive cases were included, with a mean age of 46 years, 28 male and 33 female. On analysing the genetic mutations, it turned out that 51% had GNAS mutations, 5% had AIP mutations and 44% had unknown mutations. Those with AIP mutations had a younger age of onset, larger tumour diameter, and higher nadir GH levels.

Dr Takahashi described the clinical course of a patient with gigantism and an AIP mutation. The patient was an 18- year-old male with a macroadenoma. We performed transsphenoidal surgery but IGF-1 remained high, and histological findings showed a sparsely granulated tumour. We treated him with a SSA but the tumour was resistant and IGF-1 could not be controlled. We added a dopamine agonist and the IGF-1 normalised rapidly.

Recent publications include papers on development of the Japanese version of AcroQol, enhanced oxidative stress in acromegaly, shortened telomere length, and the prevalence of colorectal cancer in acromegaly.

Our ongoing challenge in acromegaly is that there has been no optimal in vitro model for GH-producing adenoma, which hampers the discovery of drugs to treat the disease.

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Quiz

How much do you know about endocrinology?

Wouter de Herder, *Rotterdam, The Netherlands*

Q1. From which syndrome did the British painter Percy Wyndham Lewis suffer?

- **A** Acromegaly with bilateral carpal tunnel syndrome
- **B** Paint pica in the presence of severe Cushing's syndrome
- **C** Clinically non-functioning pituitary adenoma with compression of the optic chiasm
- **D** Retinal detachment associated with poorly controlled type 2 diabetes

Q2. The McKittrick Wheelock syndrome is associated with hyponatraemia and hypokalaemia. What is this caused by?

- **A** Abnormal, biologically non-active ACTH
- **B** An active secreting villous adenoma in the bowel
- **C** A hypothalamic disorder with vasopressin hypersecretion
- **D** A hypersensitivity in the thiazide-responsive element in the kidneys

Q3. Four famous researchers; Frederick Banting, Charles Best, James Collip and one other are acknowledged as world leaders in the discovery of insulin: Who is the fourth?

- **A** Philip Hench
- **B** John Macleod
- **C** Edward Kendall
- **D** Douglas MacArthur

Q4. Which athlete was diagnosed with hypothyroidism shortly before the 1996 Olympic Games in Atlanta, Georgia, and successfully treated?

- **A** Carl Lewis
- **B** Michelle Smith
- **C** Andre Agassi
- **D** Marie-Jose Perec

Q5. An anicteric 55-year-old man presented with a 1-month history of yellow discoloration of his palms and soles of his feet. What is your diagnosis?

- **A** Acromegaly
- **B** Addison's disease
- **C** Diabetes mellitus
- **D** Graves' disease
- **E** Somatostatinoma

Q6. What is the name of the first discovered gastrointestinal hormone?

- **A** Gastrin
- **B** Secretin
- **C** Pancreozymin
- **D** Cholecystokinin

Q7. The politicians Ted Heath, Helmut Schmidt and Boris Yeltsin had which endocrine disorder in common?

- **A** Primary hypothyroidism
- **B** Primary hyperparathyroidism
- **C** Zollinger-Ellison syndrome
- **D** Diabetes mellitus following chronic pancreatitis

Q8. Which disease did the painter Toulouse-Lautrec suffer from?

- **A** Achondroplasia
- **B** Pycnodysostosis
- **C** Cancan de Moulin Rouge syndrome
- **D** PLOSL

Q9. A type of thyroid tumour that was considered malignant pre-2016 is now considered benign. Which is it?

- **A** IPM
- **B** IFM
- **C** NIFTYP
- **D** NIPTF

Q10. Genetic disorders can lead to the development of phaeochromocytomas and paragangliomas. Which gene does (at present) not belong on this list?

- **A** AIP
- **B** MAX
- **C** RET
- **D** SDHP

Q11. Immune checkpoint inhibitors such as Ipilimumab and Nivolumab have recently been introduced for the treatment of melanoma, non-small cell lung cancer and renal cell cancer. Which side effect has to date not been described?

- **A** Orchitis
- **B** Adrenalitis
- **C** Hypophysitis
- **D** Thyroiditis

Q12. Recent research in the Amish community in Berne, Indiana, has demonstrated that:

- **A** KRAS mutations lead to less physical exhaustion
- **B** Tru MP1 mutations lead to early dementia
- **C** Methylation of SHOX leads to tall stature
- **D** A SERPINE1 mutation prolongs life span

Answers on next page!

Quiz answers: How much do you know about endocrinology?

Q1 The correct answer is **C**, pituitary adenoma. Post mortem examination of the brain showed that a pituitary macroadenoma had compressed the painter's visual system, causing changes in colour perception and bitemporal hemianopia.

Q2 The correct answer is **B**. Severe hyponatraemia and hypochloraemia in the presence of low urine chloride can signal the presence of a hypersecretory villous adenoma. This syndrome, described by two surgeons in Boston, Massachusetts, occurs when large villous adenomas produce quantities of electrolyte-containing mucin. Removal of the adenoma is the definitive treatment, and can be life-saving.

Q3 The correct answer is **B**, John Macleod, who was a biochemist involved in this research.

Q4 The correct answer is **A**, Carl Lewis. Five months before competing at the relatively late age of 35 in his fifth and final Olympics he was diagnosed with hypothyroidism but he was treated so successfully that he went on to win his fourth gold long-jump medal.

Q5 The correct answer is **C**, diabetes mellitus. Yelow palms and soles can occur with hypothyroidism, diabetes and carotinaemia. The discoloration may be associated with end products of advanced glycation. When this patient's diabetes management improved, so did the discoloration of the palms.

Q6 The correct answer is **B**, secretin, which was discovered by Bayliss and Starling in 1902.. Gastrin was discovered three years later. Cholecystokinin was discovered in 1928 and pancreozymin in 1940.

Q7 The correct answer is **A**, primary hypothyroidism. All three men were successfully treated.

Q8 The correct answer is **B**, pycnodysostosis. This is an inborn error of bone matrix degradation which results from deficient activity of the lysosomal protease, cathepsin K, in the osteoclasts of affected individuals. The defect leads to decreased ability of the osteoclasts to remove organic bone matrix, which leads to defective bone growth and remodelling.

Q9 The correct answer is **C**, non-invasive follicular cell thyroid neoplasm with papillary-like nuclear features.

Q10 The correct answer is **A**, AIP.

Q11 The correct answer is **A**, orchitis. A raft of side effects has been described. Endocrine-related adverse effects include diabetes insipidus, hypophysitis and hypothyroidism.

Q12 The correct answer is **D**. Khan (2017)[53] described how a null mutation in SERPINE1, which encodes plasminogen activator inhibitor 1 (PAI-1), protects against biological ageing in humans.