



# ESE INSIGHT

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**Conference report on the  
6th Annual European Meeting  
on the Management of  
Acromegaly, Istanbul, Turkey,  
25–26 September 2015**



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# Welcome to 6th Annual European Meeting on the Management of Acromegaly

## Istanbul, Turkey, 25–26 September 2015

On behalf of the scientific planning committee of the 6th Annual meeting on the Management of Acromegaly, it gives me pleasure to provide ESE members and the wider international community with the conference highlights of the recent event in Istanbul, Turkey.

Through the interactive participation of over 200 delegates during 2 days of presentations, breakout group discussions and informal networking, we advanced our understanding of the management of acromegaly.

We hope you find the conference highlights useful in your own clinical setting, especially around the following key learning points to emerge from this year's discussions.

Our thanks to the European Society of Endocrinology and The Society of Endocrinology and Metabolism of Turkey for their joint endorsement of our programme, and to Dr Rachel Arthur for her help in writing this supplement. We thank Pfizer for their continuing support of this educational event, and the distribution of this supplement.

Finally, to all speakers, moderators and the insightful contribution of our participants, thank you for making this a successful forum to advance the management of acromegaly.

**Dr Christian Strasburger, MD**  
For the Scientific Planning Committee.

### Key learning points:

- Two “new” defects of the IGF axis have been described in the past year – IGF2 and PAPP2
- The role of the endocrinologist is vital for putting lab test results into context
- When there is dissociation between biomarkers, IGF-1 may be more reliable than GH
- FIPA tumours are more aggressive than sporadic cases of pituitary adenoma
- The locus has been confirmed for X-linked acrogigantism (X-LAG)
- With advances in radiotherapy, it may in the future gain a role in an earlier phase in patient management
- GH-deficient status may be causally related to the development of non-alcoholic steatohepatitis (NASH)
- GH and IGF-1 may be applicable for the treatment of NASH
- Consensus statements are not set in stone; we follow them while exercising our own clinical judgement
- Glucose tolerance and insulin resistance are only modestly altered by SSA therapy but it is useful to monitor glucose homeostasis in these patients
- Acromegaly is associated with some cancers – colon, thyroid and breast in particular – but the excess risk is moderate
- Pituitary re-operations can be considered at any stage of the treatment protocol if control of acromegaly is inadequate, or if tumour recurrence or progression is noted
- Normalisation of the GH excess is not always the goal of repeat surgery

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# The IGF system; and assessing control of acromegaly

Dr Ron Rosenfeld from Stanford, US spoke about the fascinating IGF system. The IGF system is remarkably complex, and much of what we know about it comes from studies of IGF deficiency. A number of defects in the GH-IGF-1 axis have been observed: more than 300 cases of GH receptor defects have been recorded worldwide. In addition, 10 cases of STAT5b mutations have been recorded, plus 4 cases of IGF-1 mutations and 21 cases of IGF acid-labile subunit (ALS) mutations.

Normal fetal and childhood growth is controlled by the GH-IGF axis. Short stature arises as a result of defects at various sites along the axis, according to the level of GH secretion and sensitivity (Savage, 2010<sup>1</sup>). Dr Rosenfeld described a case of a “bioinactive, yet immunoassay-measurable IGF-I protein”. The patient was aged 55 years and had a height of 117.8cm. He had both intra-uterine and postnatal growth retardation, microcephaly, deafness and mental retardation. The patient had elevated levels of GH and IGF-1 but on IGF-1 sequencing homozygous V44M substitution was found. This resulted in defective DNA synthesis and replication.

Dominant-negative mutations of the GH-IGF axis can result in “mild” phenotypes. In a minority of cases GHI might present with mild growth failure, normal facial features and high GHBP levels. Dr Rosenfeld described the case of a girl who had a single heterozygous mutation at exon 9 of the GHR. In the GHR mutant mRNA, exon 8 was spliced directly onto exon 10.

She presented with a height of -4.2 SDS and a mild degree of GHI (IGF-I of 43 ng/ml, with the lower range of normal being 58 ng/ml). The same mutation was present in her mother and maternal grandfather, and both these individuals had a height of -4 SDS.

Two “new” defects of the IGF axis have been described in the past year – IGF2 and PAPP2. Begemann and colleagues<sup>2</sup> (2015) reported a case of paternally inherited IGF2 mutation and growth restriction. This phenotype affects only family members who have inherited the variant through paternal transmission; the mutation on the maternal allele is not expressed but these individuals are carriers. To date, one mutation and 4 cases have been reported.

Patients with PAPP2 mutations have growth failure with elevated levels of IGF-1. Whole-exome sequencing is used to sequence the genome of the patient and his first-degree relatives. PAPP2 is a pregnancy-associated protease that normally degrades IGF binding proteins 3 and 5. It regulates release of IGF-1; since the binding proteins are not degraded, they continue to hold onto the IGF and the IGF is not released to its receptor. To date, 2 mutations and 5 cases have been reported.

What is the rationale for combination GH/IGF-1 therapy? GH may have some growth-promoting actions that are independent and additive to IGF-1 effects; IGF monotherapy suppresses endogenous GH production; GH increases

## Breakout discussion I: GH and IGF-1 in diagnosis and management of acromegaly: some contentious issues

### In the first breakout session participants debated the following questions:

1. Is GH or IGF-1 more informative in the diagnosis and follow-up of acromegaly?
2. Can GH measurement be abandoned in the diagnosis and follow-up of acromegaly?
3. Are GH and IGF-1 measurements performed by an endocrine lab or are they under an endocrinologist's supervision? Who selects the methods?
4. What is the role of the endocrinologist in the assessment of GH and IGF-1?
5. Are there any problems with the normative data for GH and IGF-1 assays?

Most delegates use both GH and IGF-1 in the diagnosis of acromegaly, though some participants believed that IGF-1 was the most important lab parameter and the GH and OGTT results were not needed in diagnosis of most cases. Standardisation of measurements is important, as is their interpretation. As regards follow-up, the mode of treatment and availability of testing are both relevant aspects. And for both diagnosis and follow-up it is necessary to take into account the patient's clinical picture and any drugs that they may be taking. If the patient is not doing well then clinicians would perform more detailed investigations.

Participants agreed that GH measurements could not be abandoned, particularly in long-term follow-up. In some circumstances GH measurement is desirable, for instance to understand what is going on when there appears to be a discrepancy between test results and the clinical picture, or to evaluate compliance. There is a difference between what is described in scientific papers and what occurs in real life.

To answer question 3, most participants agreed that the laboratory decided on which assay to use, and that the clinician (regrettably) does not have much influence. Although a biochemist might be in charge of the lab, it would be ideal if the endocrinologist agreed the assay to be used with the biochemist, especially if unexpected results were obtained.

A repeat blood sample should be taken if the lab results are unexpected (in answer to question 4). The role of the endocrinologist is vital in interpretation of test results for both GH and IGF-1, to put them in a clinical context. The endocrinologist should talk to the biochemist, rather than just trust the numbers. The clinician should ideally have as much knowledge as the biochemist about the tests used, knowing about the reference values and the limitations of the assay. However, not all endocrinologists are trained in how assays work and how they are performed.

Issues with the normative data were reported for both GH and IGF-1.

production of IGFBP-3 and ALS; they have opposing metabolic effects so administering both might balance metabolic activity; it might allow once-daily dosing; and there is a trial of rhGH and rhIGF-1 co-administration. This trial showed a 2 cm increase in first year height velocity in patients treated with GH/IGF-1 combination therapy versus those treated with rhGH monotherapy (11.4 versus 9.3cm).

The GH/IGF axis continues to have many unanswered questions. Dr Rosenfeld concluded that "it is better to have unanswered questions than unquestioned answers".

The first debate concerned the best parameter for assessment of acromegaly control. The case for GH was put by Dr Annamaria Colao, from Naples; should we use GH and IGF-1 for this purpose or just IGF-1? It was probable that if we limited our observations to IGF-1 only we could miss some clinical information, she said. Recent guidelines feature measurement of GH in many clinical situations (after surgery, for instance, and when IGF-1 levels are elevated) and recommend that both GH and IGF-1 are used to determine disease control. Measurement of IGF-1 alone is not enough: clinicians need to know both IGF-1 and GH levels.

There may be discordance between GH and IGF-1 levels in the individual patient. As an example, in the early post-operative period the GH level may be normal while the IGF-1 level is raised. Apart from methodological issues with the assays, many other conditions and treatments may affect the readings obtained, such as liver disease, diabetes, radiotherapy, pregnancy and oral oestrogens.

GH and IGF-1 provide important and complementary information, said Dr Colao. GH provides a measure of tumour activity and IGF-1 a measure of overall disease activity.

Conventional and novel biomarkers of treatment outcome in patients with acromegaly give discordant results after SSA treatment compared with surgery<sup>3</sup>. Despite similar and normalised IGF-1 levels, SSA treatment was associated with less suppressed GH levels and less symptom relief as compared to

surgery. Patients had significantly better self-reported overall health after surgery, with fewer headaches and less joint pain.

Neggers (2011)<sup>4</sup> has proposed the existence of extra-hepatic acromegaly. Patients who are taking long-acting SSA whose IGF-1 levels are normalised still encounter increased GH actions in tissues other than the liver, giving rise to persistent disease activity. Pegvisomant blocks systemic GH actions but may cause further elevation in serum GH levels. Thus, it is difficult to monitor treatment using traditional biomarkers.

The case for IGF-1 was put by Dr Philippe Chanson from Paris. Normal levels of IGF-1 are markers of good control, and mortality. Elevated IGF-1 levels are associated with double the mortality of normal IGF-1 levels; normal IGF-1 is a marker of good control and co-morbidity. Clinical improvement is parallel to IGF-1 decrease with respect to appearance, tongue volume, obstructive sleep apnoea, LV mass and cardiac parameters. Prolonged treatment leads to continuing improvements.

As regards dissociation between the two biomarkers, patients with high GH/normal IGF-1 are younger, more often female, have a lower BMI, lower FBG and lower HbA1c than patients with high IGF-1 and normal GH<sup>5</sup>. Thus, IGF-1 may perhaps be more reliable than GH. High levels of IGF-1 with low GH levels often correspond to acromegaly with low (but persistent) GH output.

What are the limitations of IGF-1 measurement? Different assay methods can give different results. IGF-1 levels may be increased though the acromegaly is cured, and conversely IGF-1 levels may be normal though the acromegaly is active.

Dr Chanson described the VARIETE study<sup>6</sup>, which was designed to establish method-specific and age- and gender-adjusted reference intervals for six different assay methods using samples from 972 healthy subjects. It was concluded from this study that, even with the same reference population for different IGF-1 assays, classification between high, normal and low of patients varied between one method and another. The reference intervals for IGF-1 developed with the study are, for the six kits tested, different from those provided by the manufacturers and used routinely by laboratories. Pitfalls for interpretation of IGF-1 include: puberty, adolescence and young adulthood; uncontrolled diabetes; renal failure; liver failure; and pregnancy or oral estrogens. In these cases, clinical judgement and measurement of GH can help to classify the patient correctly.



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## Recent developments in genetics of acromegaly

Dr Liliya Rostomyan from Liege gave a presentation on new insights into the genetics of acromegaly. Most pituitary tumours are sporadic but rarely they may occur as part of a genetic syndrome: the most common example is multiple endocrine neoplasia type 1 (MEN1), which accounts for 3% of all pituitary adenomas. Other inherited causes of pituitary adenomas include CNC, MEN4, PRKACB and FIPA-AIP mutations.

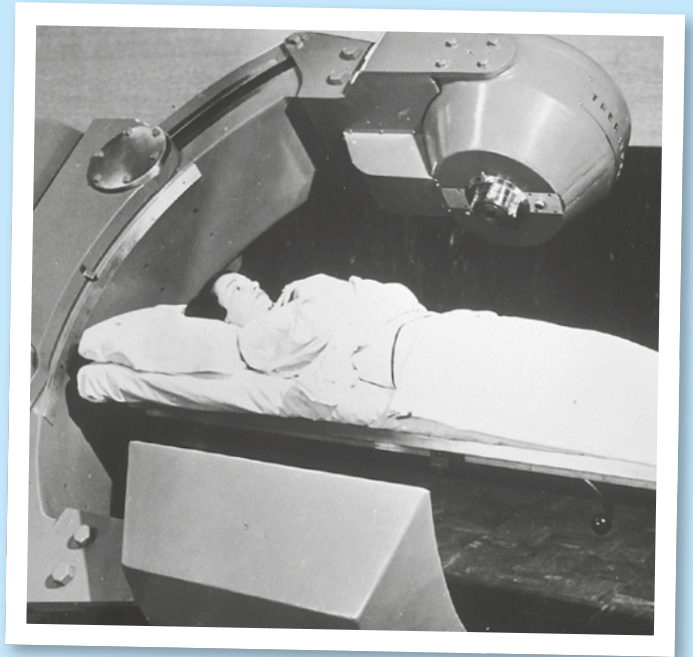
FIPA-familial causes of pituitary adenoma (other than Carney complex and MEN1) - can include all phenotypes, such as GH, PRL and ACTH, and the tumours are more aggressive than tumours from sporadic cases.

Those with AIP mutations are younger at diagnosis than those without (25 versus 38 years in two separate studies) and they have larger tumours and higher GH levels at diagnosis<sup>7</sup>. Those with mutations are more resistant to SSA treatment, with smaller decreases in GH and IGF-1 in response to treatment. The at-risk groups for mutations in AIP are individuals with FIPA, gigantism, children with pituitary adenoma and sporadic macroadenomas if younger than 30. Genetic testing is recommended for all these individuals.

A retrospective study (Rostomyan, 2015<sup>8</sup>) into pituitary gigantism was published recently. The study enrolled patients from 47 centres in 18 countries, and included 208 patients with pituitary gigantism. The multinational collaboration was set up to investigate X-linked acrogigantism (X-LAG). The results were confirmation of the locus, reduction of the number of genes to 4, and description of a new clinical syndrome. Readers are referred to Trivellin, 2014<sup>9</sup>: "Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutations" and Beckers, 2015<sup>10</sup>: "X-linked acrogigantism syndrome: clinical and therapeutic responses".

The accelerated height and weight gain started in late infancy (median age at onset of rapid growth was 12 months); the X duplication group had an earlier age of onset compared to the non-duplicated gigantism cases – 12 versus 16 years. Age at diagnosis was younger (3 versus 21 years), and most patients (71%) were female. They had higher levels of IGF-1, and frequently had co-secretion of PRL.

The genetic results of this study described by Rostomyan<sup>8</sup> show that 46% of patients had identifiable genetic causes or inherited syndromes, the most common of these being mutations of AIP. By genotype, X-LAG was seen in 14 patients, 42 patients had AIP mutations and 77 patients did not have a genetic alteration. Most X-LAG patients were female, and they were significantly younger than the other groups at onset and diagnosis of disease. Some 77% of tumours in X-LAG were macroadenomas (a smaller percentage than the other groups), and both tumour extension and tumour invasion were less common. Prolactin co-secretion was much more common, however. Currently, more than 21 cases of X-LAG have been identified by the Liege group and further results are expected soon regarding its pathophysiology and mechanisms.



## The evolution of radiotherapy

The session on modern radiotherapy in acromegaly was moderated by Dr Vera Popovic from Belgrade. In the old days, radiotherapy was considered to be the last approach but advances in technology may mean that radiotherapy can be moved to an earlier phase in patient management, she said. The session commenced with a film on new technical modalities and classes, presented by Dr Enis Oszar from Istanbul.

New radiotherapy techniques include 3-D conformal and intensity-modulated radiotherapy (IMRT), volumetric modulated Arc radiotherapy, stereotactic radiotherapy and radiosurgery, image-guided radiotherapy and 3-D MRG-guided brachytherapy. The rationale behind new technology is better tumour coverage, dose escalation, maximum protection of normal tissue, and decreased overall treatment time. Stereotactic radiosurgery is an alternative to surgery. It allows tumours to be ablated using stereotactic methods. It is usually used for benign lesions and lesions to the cranium. A single, high dose (18-25 Gy) is given.

Stereotactic radiotherapy means that larger tumours (>3cm) and those close to sensitive structures can be treated. In addition, previously irradiated sites can be treated again. Two to five fractions are given for Cyberknife and 2-30 for Linac-based systems.

The efficacy of gamma knife (GK) surgery in acromegaly was discussed by Dr Marco Losa from Milan. Gamma knife equipment allows better dose planning. In the 1960s up to 100Gy were administered but since 1990 the dose is typically 25-30 Gy.

Normalisation of IGF-1 level is the most important variable to define remission of disease after radiosurgery; regulation of GH secretion may remain abnormal for a longer period. A review of the literature showed a remission rate of 17-67%

after gamma knife, with remission rates at 5 years ranging from 29% to 60%. A low burden of disease activity, as reflected by low GH and IGF-1 levels before radiosurgery, is predictive of the likelihood of remission after gamma knife treatment.

Papers report shrinkage of tumour in at least 42% of cases (92% in one paper<sup>11</sup>). Another advantage is that gamma knife surgery can be repeated. Endocrine Society clinical practice guidelines from 2014 recommend that radiation therapy may be considered at any point following incomplete surgery. Selection of the right patient is the key to success.

The side effects of radiotherapy in acromegaly were discussed by Dr Nienke Biermasz from Leiden University Medical Centre. To address this, we have to extrapolate data from previous studies using older radiotherapy methods and combine them with the more recent "high precision" delivery.

A number of aspects of radiotherapy for acromegaly have evolved. First, the indications have changed; second, there have been treatment advances; and third, radiotherapy techniques have changed.

There is a clear pathophysiological basis for RT-induced damage. The mechanism for the side effects of radiation is radiation damage to the surrounding tissue. This induces apoptosis and reproductive cell death because of DNA damage, depending on the cell proliferation rate, the dose and the technique. Observed adverse effects include mortality, risk of neoplasm, impaired cognitive function and impaired quality of life. However, it has to be determined whether these are the side effects of RT or complications of the disease itself. Hypopituitarism and cranial nerve damage are side effects unique to RT but the causation of other adverse effects is less clear.

Does RT result in hypopituitarism? After 3D conformal fractionated RT, 50-54% hypopituitarism was reported 15 years ago but by the year 2012 the incidence was reported as 6% using RT closer to current practice, but with shorter follow-up duration. After RT hormone levels gradually decay. New RT techniques theoretically have some advantages since hypopituitarism depends on the dose of radiation to the pituitary gland. The dose at the pituitary stalk is an independent risk factor for hypopituitarism. What of cranial and optic nerve damage? Single fractionated radiosurgery gives a risk below 4%, with the risk being dependent on the margin. Risk factors include previous RT, the dose of radiation and the relation of the tumour to the optic nerve. With respect to mortality, disease control, co-morbidity such as diabetes and hypertension, hypopituitarism and RT are all factors of influence. Although patients who receive RT appear to be at significantly greater risk of dying from cerebrovascular disease, RT per se has not been confirmed as an independent risk factor.

Low-dose RT can cause secondary brain tumours but the risk is very small in pituitary disease. After single fraction RT the incidence was 0.002%, but there are no long-term data.

No strong conclusions can be drawn about whether RT affects quality of life. Patients may complain of diffuse cognitive impairment; some abnormalities may be observed but the data are conflicting.

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"A number of aspects of radiotherapy for acromegaly have evolved. First, the indications have changed; second, there have been treatment advances; and third, radiotherapy techniques have changed."

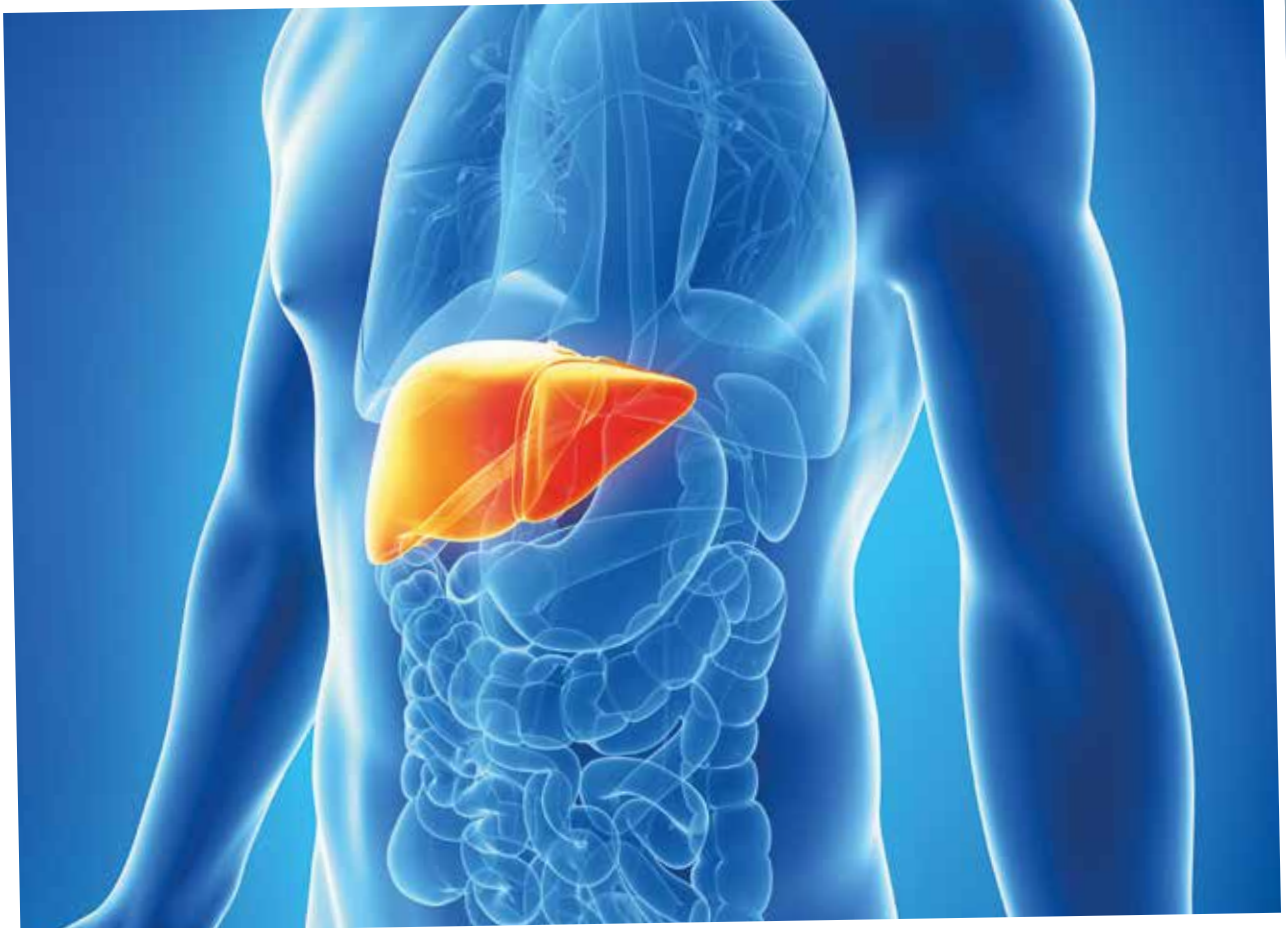
Dr Frederic Castinetti from Marseille discussed the efficacy of recent radiation techniques. The majority of studies published to date on "conventional" RT are based on patients who were treated 20 years ago. The conventional wisdom is that RT is highly effective, that it carries a high risk of toxicity and that its efficacy is largely delayed. For example, Jenkins (2006)<sup>12</sup> showed that the technique carried 60-80% efficacy in normalising GH levels if you waited long enough (10-20 years).

Dr Castinetti presented a study that compared FSRT (Fractionated Stereotactic Radiotherapy) against GK (Gamma Knife). FSRT theoretically has the advantage of stereotactic accuracy with fewer adverse effects because of the dose fractionation. Patients were followed up for a median 5 years. A higher median dose was given with FSRT. The two techniques had very similar antitumour efficacy (88-90%) and mean time to remission (24-26 months). Hypopituitarism was seen in 20% of patients in both groups but no patient in the FSRT group suffered a visual defect after treatment. A number of studies have evaluated FSRT; the published results are tumour control in 95% of patients and hormone control in 45%.

Proton beam therapy is used mainly in the US. In theory it has fewer adverse effects because the maximal dose does not diffuse outside the target. In one study of 50 acromegaly patients (Watson, 2014)<sup>13</sup> after a mean follow-up of 57 months some 45% of patients had new pituitary deficiency (correlated with target volume). Proton beam therapy achieved 100% tumour control, and hormone normalisation was 45-55% at 5 years. Another study found that about 20-40% of patients will be controlled after RT with an unchanged or decreased dose of SSA.

### In conclusion:

- New radiation techniques are not the same as older techniques
- They are effective in controlling hormone secretion and tumour volume in some patients.



## GH and liver disease

Dr Yutaka Takahashi from Kobe, Japan, described the essential role of GH and IGF-1 in the liver. Blockade of the GH receptor in the liver induces fatty accumulation. Non-alcoholic steatohepatitis (NASH) is a progressive disease that shows inflammation and fibrosis in addition to steatosis. In 30-50% of cases it is progressive, and in 5-20% of cases it develops into liver cirrhosis or liver cell carcinoma. GH-deficient status may be causally related to the development of NASH.

In one paper (Nishizawa, 2012)<sup>14</sup>, the prevalence of NAFLD in patients with adult growth hormone deficiency (AGHD) was increased 6.4-fold compared with the prevalence in controls (77% vs. 12%;  $p < 0.0001$ ). Results of liver biopsies performed in 16 patients with AGHD revealed that at least 21% of these patients had NASH. Nishizawa also studied the effect of GH replacement therapy. After six months, there were significant improvements in the liver enzymes AST, ALT and gamma GT. GH replacement therapy also ameliorated the histological changes, with improvements in steatosis and fibrosis.

A total of 31 patients who had GH replacement therapy for at least 24 months were compared with 19 age-, gender- and BMI-matched controls who had not undergone GH replacement therapy<sup>15</sup>. Significant improvements in AST and ALT levels were seen in patients who had had GH replacement therapy compared to controls.

As regards the possible therapeutic application of GH/IGF-1 for NASH:

- GH/IGF-1 plays an important role in prevention of the development of NASH in GH-deficient states
- Pioglitazone, vitamin E and the FXR agonist obeticholic acid have been reported to improve the histological appearance of NASH though the effect on fibrosis is limited/controversial
- Fibrosis determines the prognosis

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"Results of liver biopsies performed in 16 patients with AGHD revealed that at least 21% of these patients had NASH."

## Interpreting consensus statements in practice

Dr Ariel Barkan (Professor of Medicine and Neurosurgery from the University of Michigan) addressed the issue "What do we do with all the consensus statements?" The first consensus statement on criteria for cure of acromegaly was published in the JCEM in the year 2000. Since that time many updates have been published, and a lot of things have changed since 2000.

The diagnostic and surveillance criteria of "cure" of acromegaly, more recently "control", have changed, for example. Better assays, and more widespread use of MRI, made our understanding of acromegaly more sophisticated during that time period.

In 2012, a paper described an acromegalic giant in whom GH levels were normal, so-called micromegaly. Investigation of similar patients revealed that mean GH levels were not significantly raised but that IGF-1 levels were raised three-fold. Monitoring of GH levels over time produced the explanation. In normal patients, GH sinks to almost undetectable levels but this is not the case in micromegaly. It is not the mean GH level that determines who develops acromegaly but rather the nadir GH level that selectively determines IGF-1 levels. If baseline GH rises to constantly above 0.2 ng/ml then we become clinically and biochemically acromegalic.

How reliable are GH sampling models? A single measurement of GH is of little use in diagnosis and surveillance – hourly samples over a period of nine hours are needed to derive useful information.

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"Surgical debulking improves the efficacy of SRL. Endoscopic surgery with extended skull-base approach is now used for treatment of pituitary tumours."

What is the place of surgery for acromegaly? In 2000, surgery was first-line treatment except in the case of medical contra-indications or refusal. In 2014, surgery was still first-line but debulking was recommended for inoperable tumours and re-operation for intrasellar remnants. One reason for the change of recommendation is the discovery that surgical debulking improves the efficacy of subsequent medical treatment such as SRL. Endoscopic surgery with extended skull-base approach is now used for treatment of pituitary tumours. We have a significantly improved aggressive surgical tool, and we should make use of it.

Medical treatment of acromegaly in 2000 comprised SRLs, dopamine agonists rarely (which were ineffective) and pegvisomant (for which there were no clinical data). By the year 2014 the armamentarium included SRLs, cabergoline, pegvisomant, oral octreotide and other novel approaches. Pasireotide has been recently approved.

Acromegaly patients achieve remission following radiosurgery in about 40% of cases. However, the success of SRS depends on pre-treatment GH levels: the apparent higher efficacy and faster effect of gamma knife radiosurgery are likely to be due to selection bias rather than inherent superiority of the gamma knife.

Is pre-treatment with SRLs beneficial? One problem is that studies to address this question have not been randomised. So although some studies suggest that pre-treatment doubles the rate of cure, the difference seen at 3 months disappears at 12 months, implying that the apparent improvement was actually a carry-over effect of SRLs.





## A case-oriented approach to metabolism

A case-oriented approach to metabolism in acromegaly was moderated by Dr AJ van der Lely. He presented the case of Mr Holland, a 31-year-old untreated patient with acromegaly who had visual disturbance. A scan showed a tumour impinging on the optic chiasm. He had TSS but was left with a significant remnant and elevated GH and IGF-1.

He is given octreotide; what effects do the “old” SSAs have on blood sugar? Dr Silvia Grottoli explained that the UKPDS study<sup>16</sup> underlined the importance of glycaemia. In patients with type 2 diabetes the risk of microvascular and macrovascular complications was strongly associated with previous hyperglycaemia. Any reduction in glycosylated haemoglobin is likely to reduce the risk of complications: the lowest risk was seen in patients with HbA1c values in the normal range. As regards the link between acromegaly and diabetes, a family history of diabetes, age, high levels of GH and IGF-1 and duration of disease are considered to be the major risk factors. GH induces hyperglycaemia through various mechanisms, including increased lipolysis, raised levels of FFA and glycerol, increased gluconeogenesis, lowered glucose uptake and oxidation in muscle, and induction of insulin resistance.

### In conclusion:

- Conventional SSA were initially suspected of worsening glucose tolerance in acromegaly (by suppressing plasma insulin concentrations)
- Subsequent studies suggested that glucose tolerance and insulin resistance were only modestly altered by SSA therapy
- It is useful to monitor glucose homeostasis in all patients on SSA therapy, regardless of the pre-existing metabolic condition, especially in those with uncontrolled GH and IGF-1 levels.

Mr Holland is given pasireotide. Dr Anton Luger discussed the link between this drug and diabetes. Dr Luger described data from the PAOLA study (Gadelha, 2014)<sup>17</sup>, which investigated 198 patients with long-standing severe acromegaly treated with octreotide or lanreotide for at least six months. The patients were given 40mg or 60mg pasireotide or they continued with their previous treatment.

Pasireotide 60mg was more effective in normalising GH and IGF-1 (20%, versus 15% with pasireotide 40mg). However, hyperglycaemia was observed more frequently in patients with diabetes who were treated with pasireotide (71% with 40mg pasireotide; 70% with 60mg pasireotide). With pasireotide, normalisation of overall and post-surgery GH and IGF-1 was achieved more often than with control.

To investigate the mechanism of pasireotide-induced hyperglycaemia, OGTT, hyperglycemic clamp and hyperinsulinemic-euglycemic clamp tests were performed in 45 healthy male volunteers at baseline and during treatment with pasireotide.<sup>18</sup> The doses, administered subcutaneously twice a day, were 600µg and 900µg; the 1200µg dose was discontinued since it gave so many G-I adverse effects.



Pasireotide was associated with decreases in insulin secretion and incretin hormone responses.

In healthy volunteers, vildagliptin and liraglutide were the most effective measures to control plasma glucose induced by pasireotide. So the main adverse effects of pasireotide are similar to those of octreotide and lanreotide and are related to the G-I tract and carbohydrate metabolism. However, they are observed more frequently and are more severe with pasireotide treatment. Third, Mr Holland is given pegvisomant. How does this affect blood sugar? Dr Jens Otto Jorgensen said that there is a precarious balance in glucose homeostasis in active acromegaly. Patients have GH-induced hepatic and peripheral insulin resistance, which is offset by increased lean body mass, decreased fat mass and possibly by improved VO<sub>2</sub>-max. Poor lifestyle and bad genes make the patient more likely to develop diabetes.

Dr Jorgensen presented a paper (Lindberg-Larsen 2007)<sup>19</sup> which studied the impact of pegvisomant on substrate metabolism and insulin sensitivity in patients with acromegaly. Both basal serum insulin and plasma glucose levels fell after treatment. Both peripheral and hepatic insulin sensitivity were improved, and this was associated with a decrease in resting energy expenditure. A small but significant increase in total body fat and decrease in lean body mass were observed, which might tend to worsen insulin sensitivity. Dr Jorgensen considered pegvisomant to be neutral with regard to causing diabetes.

Treatment of acromegaly patients exacerbated by concomitant type 2 diabetes requires higher pegvisomant dosage to normalise IGF-1. Dr Jorgensen concluded that pegvisomant treatment in acromegaly improves hepatic and peripheral insulin sensitivity via specific GH blockade in these tissues. Correction of GH hypersecretion also increases fat mass and decreases lean body mass, but the net effect of pegvisomant is favourable.

## Debate: does acromegaly give you cancer?

The second debate of the meeting discussed whether acromegaly gives you cancer. The argument for the statement was presented by Dr Massimo Terzolo from the University of Turin. Why might circulating levels of IGF-1 be related to cancer risk, he asked. There are two hypotheses: one, that higher IGF-1 levels favour the emergence of a malignant clone and the other, that they favour more rapid proliferation of early cancers.

In a meta-analysis that examined possible associations between IGF-1 and IGFBP3 and cancer in the general population, IGF-1 levels were found to be associated with a moderate increase in cancer of the colon, prostate and breast.

Data on colon cancer and acromegaly depend on results from endoscopic studies. Findings are consistent, showing a moderately increased (doubled) risk for primary colon adenomas in patients with acromegaly. These adenomatous polyps are likely to transform to adenocarcinomas in time. Colon cancer is a less frequent event but studies are homogeneous in showing an increased risk in patients with acromegaly. Most studies showed no association between GH and IGF-1 levels and prevalence of colon neoplasia. Higher IGF-1 levels are associated with a risk of recurrence. Acromegaly confers a moderate risk for colon cancer, similar to a strong family history.

On the basis of these results, guidelines make the recommendation that patients with acromegaly should be offered colonoscopy screening at diagnosis; and that they should be offered regular screening endoscopy from the age of 40 years.

The risk of thyroid cancer is also raised in patients with acromegaly. The estimated risk is less precise because patient numbers are smaller but the risk has consistently been shown to be elevated. A study from Spain, from an iodine-sufficient area, looked at benign and malignant nodular thyroid disease in acromegaly. The study population consisted of 123 patients and 50 matched controls. Results showed that goitre (24.9% vs. 8.3%), nodular thyroid disease (55.5% vs. 30.0%) and papillary thyroid cancer (2.4% vs. 0%) were more common in acromegaly patients than in controls.

Dr Terzolo presented data from 1,512 Italian patients diagnosed with acromegaly between 1980 and 2002 and with a mean follow-up time of 10 years.<sup>20</sup> Important predictors of mortality were age, IGF-1 level at diagnosis, GH at follow-up, malignancy and radiotherapy. Overall SMR was 1.13 and active disease SMR was 1.93. Among women, all cancers, breast, colorectal and thyroid cancers were observed more frequently than expected; among men, all cancers, colorectal, kidney and thyroid cancers were more frequent. A multivariate analysis showed that age, family history of cancer, and disease duration were predictors of cancer.

Dr Terzolo concluded that the excess risk is moderate, about twice that of the general population. Longer follow-up is needed to allow firm conclusions to be drawn.

The argument against the statement was given by Dr John Ayuk from the University of Birmingham.

Early epidemiological studies suggested that cancer-related mortality was increased in females and males. The cancers thought to be associated with acromegaly were breast cancer, colon, prostate and thyroid cancer, and haematological malignancies. However, data from later epidemiological studies disputed this cancer-related mortality risk. There was no overall increase in mortality although the Orme study<sup>21</sup>, using data from an acromegaly register, showed a modest rise in female breast cancer (SMR 1.60) and colon cancer (SMR 2.47).

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"Data on colon cancer and acromegaly depend on results from endoscopic studies. Findings are consistent, showing a moderately increased (doubled) risk for primary colon adenomas in patients with acromegaly."

There is a correlation between circulating levels of IGF-1 and the risk of breast and prostate cancer, as shown by Furstenberger and Semm (2002)<sup>22</sup>. There may be alternative explanations for elevated serum IGF-1 levels in cancer patients. They may be due to ascertainment bias (IGF-1 causes symptomatic benign tissue hyperplasia, leading to investigation and diagnosis of asymptomatic cancers); or elevated serum IGF-1 in cancer patients may originate from within the tumour, as suggested from animal studies; or serum IGF-1 may be a surrogate marker for tissue IGF-1 levels, not under GH control.

Dr Ayuk presented examples of how the association between acromegaly and cancer should be investigated. He commended Manchester data (Renehan, 2000) which described the prevalence and characteristics of colorectal neoplasia in acromegaly. A graph plotting the cumulative incidence of colorectal cancer by age in groups with known hereditary predisposition and acromegaly in comparison with the general population shows that acromegaly confers a risk similar to that of a strong family history. The greatest risk factors for the development of cancer in patients with acromegaly are age and family history – but that is the case for all cancers. He concluded by reminding attendees that there is no direct proven relationship between acromegaly and malignant disease.

## Control of the somatotrophic axis

Dr Patrice Mollard from Montpellier described the complicated control of the somatotrophic axis. In the 1980s the model was simple, he said, but it has changed since then to a more complicated scheme, with postulated involvement of somatostatin-expressing neurones, GHRH-expressing neurones, somatotrophs and gut hormones. Are mice suitable models for assessment of GH release relative to human physiology and pathology (acromegaly)? They do seem to be helpful in showing how GH is generated. GHRH can be targeted very efficiently, and manipulated.

Long capillary loops which ascend into the arcuate nucleus of the hypothalamus have been demonstrated in mice and in humans (by post mortem injections). Dr Mollard described the development of imaging techniques to investigate their function. A new, highly sensitive mGH ELISA has been developed. Mice only have 2 or 3ml of blood, but a tail blood sampling method has been worked out. The new ELISA only needs a couple of  $\mu$ l so this allows longitudinal studies to be performed in the same mouse and it allows estimation of GH secretion rates.

To examine the large-scale 3D organisation of GH cells, and how the population of GH cells generates pulses, transgenic mice were used. Surprisingly, imaging showed not that the pituitary was a patchwork of endocrine cells but that the cells formed a network, each cell in contact with the others. To investigate further GH rhythms, optogenetic manipulation

of GHRH hormones in GHRH-Cre mice was used. Neurones can be switched on and off on demand, to investigate their function and to estimate the rate of hormone release.

It is assumed that acromegaly is based on disorganisation of the GH cell network and GH secretion. We now have the ability to use genetically modified mouse models to understand how GH is released into the blood, and we can use these models to study the hypothalamus and pituitary. The techniques permit study of the 3D organisation of cells, and the manipulation and monitoring of cell activities in vivo. This should progress our understanding of how pituitary secretion is disorganised in acromegaly.

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"Long capillary loops which ascend into the arcuate nucleus of the hypothalamus have been demonstrated in mice and in humans."

## Breakout discussion II: Approaches to screening for neoplasms

**The second breakout group discussed the following questions:**

1. Which work-up should usually be performed in patients with acromegaly to rule out neoplasms (a) at diagnosis and (b) at follow-up?
2. At your centre, do you systematically screen for neoplasms in patients with acromegaly?
3. Does only colon cancer, or do also other neoplastic diseases, need to be ruled out in the clinical work-up of patients with acromegaly?
4. Can any of the mechanisms described by Dr Mollard lead to somatotroph adenoma development?

In response to questions 1 and 2, respondents from most countries performed colonoscopy at diagnosis though some doctors waited a few months before doing this so that patients were not overloaded at diagnosis, and others only performed colonoscopy in patients over the age of 40 years. In young patients, genetic causes of acromegaly needed to be considered; in elderly patients, disease burden and risk factors needed to be considered. Some practitioners performed screening procedures if there was a strong family history and others only performed them if clinical examination suggested that they were appropriate.

In addition to screening for colorectal cancer, some doctors screened their patients for possible breast, prostate and thyroid cancer, the last depending on whether the patient was living in an iodine-sufficient or –deficient area. Other doctors preferred to follow national cancer prevention guidelines.

Follow-up investigations, and their frequency, depended on the initial findings. Some would not screen again if the initial findings were unremarkable, some followed national routine screening programmes. If the GH or IGF-1 levels remained elevated then some doctors would consider screening again. Concerns were raised about lack of outcome studies and about over-investigation.

Some participants considered the phrasing of question 3 to be controversial since it implied that colon cancer needed to be ruled out. Some participants said they were becoming more conservative in screening for thyroid and prostate cancer.

As regards question 4, delegates mostly agreed that although the presentation had been stimulating, they were waiting for further evidence before committing themselves. It was difficult to understand how the studies presented could explain somatotroph development, particularly since no mechanism was given for the pathophysiology of adenoma development. It was recognised, however, that there were important genetic and epigenetic factors related to cancer in acromegaly.

## Indications for re-operation in acromegaly patients

Dr Michael Buchfelder (Professor and chairman of neurosurgery, University of Erlangen-Nuremberg) discussed the indications for re-operation in patients with acromegaly. There are no particular recommendations on repeat surgery in the guidelines but possible indications for re-operation might include persistent disease after primary surgery, recurrence of problems with disease control.

He presented four cases. The first case was a patient with residual intrasellar tumour; the objective was to resect the tumour completely. The second case was a patient with controlled acromegaly on biochemistry but in whom tumour size was still increasing; the objective was to enable gamma knife treatment. The third case was a 20 year old woman with bitemporal hemianopia; the objective was to decompress the optic system. The fourth case was a patient with persisting acromegaly: the objective was to debulk the tumour.

Dr Buchfelder summarised the indications for re-operation by making the following points:

- Pituitary re-operations do not have a fixed place in treatment algorithms for acromegaly
- They can be considered at any stage of the treatment protocol if control of acromegaly is inadequate, or tumour recurrence or progression is noted
- The "success rate" depends largely on patient selection and on the indications for repeat surgery
- Normalisation of the GH excess is not always the goal of treatment
- The complication rate is slightly increased in comparison to primary surgery
- Only a multidisciplinary team can decide the correct place for a re-operation, and this is important in achieving the optimal outcome



"There are no particular recommendations on repeat surgery in the guidelines but possible indications for re-operation might include persistent disease after primary surgery, recurrence of problems with disease control."

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