



ESE News INSIGHT

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**Conference report on the
5th Annual European Meeting on
the Management of Acromegaly
Lisbon, Portugal, 3–4 October 2014**



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5th Annual European Meeting on the Management of Acromegaly

Lisbon, Portugal, 3–4 October 2014

Christian Strasburger (Berlin, Germany) welcomed the 215 delegates to Lisbon and opened the meeting, on behalf of the Scientific Planning Committee. In his introduction, he encouraged everyone to share their experience and engage actively in the debates, the main sessions and the breakout sessions.

DEBATE: Routine radiotherapy for acromegaly should be forbidden

In the first Oxford-style debate of the conference, the case for use of radiotherapy was put by John Ayuk (Birmingham, UK) and the case against by John Wass (Oxford, UK).

The case in favour of radiotherapy

What are the indications for pituitary radiotherapy?

- Surgery is contraindicated, declined or has proved unsuccessful
- Medical treatment is not tolerated
- There is persistent or recurrent hypersecretion or tumour growth despite surgery or medical treatment
- Aggressive tumours

Conventional radiotherapy is effective in lowering growth hormone (GH) levels.¹ The discipline of radiotherapy has moved on, and results have improved. For example, one paper looked at five studies utilising fractionated stereotactic radiotherapy; the authors followed 115 patients with GH-secreting pituitary tumours for a median period of 54 months. Tumour growth control was achieved in 97% of patients, and median biochemical remission was 40%. Another paper analysed 29 studies of stereotactic radiosurgery that followed 1215 patients for a median of 50.6 months. Tumour growth control was achieved in 98% and biochemical remission ranged from 17 to 82%. Dr Ayuk concluded that routine radiotherapy for acromegaly should definitely not be forbidden – it features in the Acromegaly Consensus Group 2009 management algorithm.

The case against

Professor Wass countered by saying that it was rarely necessary to give radiotherapy, that it was not invariably effective and that it almost always had side effects. The side effects of pituitary radiotherapy include hypopituitarism, visual impairment, cerebrovascular disease, radiation oncogenesis and neurocognitive changes.

Recurrence in acromegaly is actually very rare: 2–3% or 5.4% in two studies. Recurrence of pituitary adenoma is rare once the tumour is removed with surgery, and therefore radiotherapy is not often needed. At 10 years, radiotherapy is only effective at lowering insulin-like growth factor-1 levels to normal in 63% of patients, and stereotactic radiotherapy for acromegaly achieves an overall remission rate of 80% at 10 years.

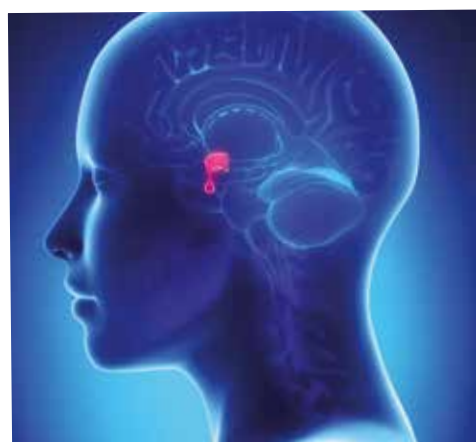
Professor Wass commented that almost every patient who has pituitary radiotherapy develops a complication. Data on development of new hypopituitarism at 10 years following pituitary radiotherapy showed that 70% had gonadotrophin deficiency, 54% had adrenocorticotrophin deficiency and 38% had thyrotrophin deficiency.²

Does pituitary radiotherapy increase the risk of stroke? Professor Wass referred to a paper published by Dr Ayuk in 2012,³ which reported that all-cause mortality (standardised mortality ratio (SMR) 1.58, $P=0.005$) and cerebrovascular mortality (SMR 4.42, $P=0.005$) were raised in patients with acromegaly who had received pituitary radiotherapy.

Audience comments

The audience were invited to comment on the presentations. For aggressive tumours not controlled by surgery, radiotherapy might be indicated. Use of radiotherapy might avoid 30 years of drug treatment; this should be discussed with young patients in order to individualise the treatment decisions. In some places, drug therapy for acromegaly is not affordable, so conventional radiotherapy should be considered. Delegates were invited to vote for and against the motion. The numbers for and against were so close that it was impossible to decide.

In the discussion at the first breakout session, major reasons given for not using radiotherapy were: if the tumour was close to the optic chiasma, or if the patient was pregnant or hoping to become pregnant. Additionally, the long term cost–benefit had not been evaluated.



Environmental pollutants and pituitary tumorigenesis

Salvatore Cannavò (Messina, Italy) said that an unusually high number of acromegaly patients come from the same small, highly polluted, area of Messina, Sicily. From a general population of 654 601 individuals, there are 60 acromegalic patients, which equates to a prevalence of 97 patients per million inhabitants.

The zones of Messina province were subdivided into four areas according to geography and industrial density. In the area of low industrial density, the prevalence of acromegaly was 26 cases per million, while the figures for the areas with medium-to-low industrial density were higher. For the most highly polluted area (with an oil refinery, steel plant, thermoelectric power station and lead recovery plant), the prevalence was 210 cases per million.⁴ Atmospheric analysis showed there to be high levels of non-methane hydrocarbons, including benzene and toluene, and volatile organic compounds.

The aryl hydrocarbon receptor (AHR) has a role in regulation of cell–cell contact and tumour growth. The AHR has been considered a major regulator of xenobiotic-induced carcinogenesis, but increasing epidemiological and experimental animal data provide substantial support for an association between abnormal AHR function and cancer.

Professor Cannavò and colleagues have reported increased frequency of the rs2066853 variant of the AHR gene in patients with acromegaly.⁵ Several single nucleotide polymorphisms (SNPs) have been found, and they are associated with increased

risk of tumours, including thyroid and bladder cancer. Patients with this variant have higher insulin-like growth factor-1 levels and a higher rate of cavernous sinus invasion. The same SNP in human gliomas is associated with higher levels of polycyclic aromatic hydrocarbon-DNA adducts and higher invasiveness of the tumour.

Cats that spontaneously develop acromegaly and type 2 diabetes have been observed in Sicily. They are exposed to the same environmental pollutants, and can be considered signals of the effects of these substances on babies and toddlers.

The critical questions in this area are:

- Can pollutant exposure increase the risk of developing cancer?
- Can this susceptibility be related to a genetic predisposition?
- Can exposure to pollutants cause epigenetic variation?
- Can exposure to pollutants increase tumour aggressiveness?
- Can exposure to pollutants modify drug sensitivity?

Audience comments

In the first breakout session, all groups agreed that the question ‘Do you consider environmental pollutants a real clinical problem in endocrinology?’ was important, but said that more data are needed since the case is at present unproven.

Acromegaly: a perspective from Portugal

Data from Portugal were presented by Davide Carvalho (Porto, Portugal). The country has a resident population of 10.5 million people, of whom 51.6% are female.

In 2004, the incidence and prevalence of acromegaly were 2.9 and 56.5 cases per million respectively. The mean age at diagnosis was 46 years, and 70% of patients were female. In 2013, the number of cases was 42, equivalent to 4.1 cases per million. Mean age at diagnosis was 50.6 years, 55% of patients were women, and the delay in diagnosis was 6.9±5.7 years.

Imaging data show that 70% of cases were macroadenomas, with cavernous sinus invasion in 50% of cases. Signs and symptoms were headache and overgrowth of the extremities ($n=12$), acromegalic face or diabetes/metabolic syndrome ($n=6$) and, less frequently, sleep apnoea, carpal tunnel syndrome etc. Some 36 patients had surgery and 4 had medical therapy as their first treatment modality; 50% of patients were controlled. Adjuvant therapy consisted of surgery ($n=3$), somatostatin analogues ($n=5$), dopamine agonists ($n=4$) and radiotherapy ($n=2$). In all, 24 patients were treated with pegvisomant, at an average dose of 15mg.

Professor Carvalho summarised the country perspective of Portugal as follows:

- There are too many surgical centres for successful management of acromegaly patients. The recommendation is that neurosurgeons should perform at least 50 cases per annum for the best results

- There are good medical treatments for acromegaly, and good results with the drugs employed
- Acromegaly-associated genes are increasingly described, which increases our knowledge of tumorigenesis
- Patients with slight clinical features are being described. They may not have the typical features of acromegaly but they allow us to diagnose more patients if we look carefully

Breakout discussion I

The majority of those involved in the discussion at the first breakout session agreed that, after 10 years of clinical experience, pegvisomant met their expectations. Some thought that 85% of patients achieved full remission; others thought that the efficacy was closer to 60 or 70% and that control was lost over time. Positive results were obtained with high doses of the drug. On the whole the drug was well-tolerated. There was a positive impact on patients' body image and quality of life.

Negative aspects included concern that the drug might not control tumour growth, and that it was a treatment rather than a cure. Some patients struggled with daily injections, some still needed radiotherapy, and the cost of the drug was an issue.

Management of aggressive pituitary tumours

This interdisciplinary discussion included speakers John Wass (Oxford, UK), Michael Buchfelder (Erlangen, Germany) and Jean-François Bonneville (Besançon, France). It was moderated by Vera Popovic (Belgrade, Serbia).

It is not certain whether evolution of pituitary tumours is a multi-step progression or whether they occur as a *de novo* transformation. An aggressive tumour is defined by its clinical behaviour, including:

- Massive invasion of the surrounding tissue
- Rapid growth, large size (proliferation)
- A tendency to recur even after initially successful treatment
- Resistance to conventional therapy (medical or radiotherapy)
- Potentially life-threatening effects

Invasiveness is defined by radiological features (invasion of the sphenoid and cavernous sinus), as well as surgical and histopathological findings.

Radiology

Dr Bonneville considered the radiological criteria for an aggressive pituitary adenoma. These may include rapid growth or recurrence, extension beyond a natural barrier, and metastases (carcinomas). Serial magnetic resonance images are needed, and they must be compatible; this can be achieved using markers.

The sphenoid sinus and the cavernous sinus are barriers to tumour growth. If the sellar floor is smooth and merely displaced then the tumour is unlikely to be invasive, but acute changes in the sellar floor denote invasion. Similarly, an invasive tumour may rupture the internal wall of the cavernous sinus.

Combining treatment modalities

The main restriction on aggressive surgery for such tumours is their invasive behaviour, said Professor Buchfelder. If the sphenoid sinus mucosa has been infiltrated and the skull base bone has invasive adenoma deposits then invasion cannot be cured by cutting. Even small tumours can be invasive, but there is a correlation with size: 2% of microadenomas are invasive, compared with 80% of giant adenomas. With aggressive tumours, total resection is frequently not possible, and so debulking surgery is used.

Available therapies are trans-sphenoidal and transcranial surgery, hormone inhibition with dopamine agonists and somatostatin analogues, radiotherapy using fractionated irradiation or Gamma Knife®, and chemotherapy with temozolomide. All treatment modalities are needed, especially for aggressive tumours.

Adjunctive techniques include endoscope-assisted surgery, neuronavigation and intra-operative imaging with magnetic resonance imaging (MRI) and ultrasound. The goals of surgery are to decrease tumour mass as much as possible, to decompress the visual pathways, to reduce hormone oversecretion, to maintain normal pituitary function and to avoid complications. One danger of over-aggressive surgery is rupture of the cavernous segment of the internal carotid artery.

Radiotherapy can reduce tumour growth, and post-operatively can reduce the recurrence rate, especially in patients with non-functioning adenomas.



Summarising the surgical approach to aggressive tumours, he said they confront the surgeon with various problems, should not be underestimated as a potential threat to the patient's life, need all available combinations of therapies, and require careful follow-up with repeat MRI and endocrine evaluations.

A role for temozolomide

Temozolomide is an oral alkylating agent. When used to treat pituitary carcinomas and aggressive tumours, hormone response was seen in 73% of prolactinomas, 67% of adrenocorticotrophin-secreting tumours and 33% of growth hormone (GH)-secreting tumours. Response was evident in the first 3 months. More data are needed from prospective trials, which are ongoing. It is used for glioblastoma multiforme and is well-tolerated.

Consideration of the patients' O⁶-methylguanine-DNA methyltransferase (MGMT; a DNA repair protein) status has shown that those with low MGMT on immunohistochemistry have a 70% response rate to temozolomide, but those with high MGMT do not respond. Further work is required on dose regime and duration, and on possible dual therapy with bevacizumab.

Another experimental approach is peptide receptor radionuclide therapy (PRRT) with ¹¹¹In-DTPA-octreotide in patients resistant to other therapy.

Prognosis

A risk factor score (maximum 13) has been developed for the factors involved in the prognosis of acromegaly:

- Histology sparsely granulated
- MRI T2 hyperintense
- Younger age
- Ki-67 >3%
- Higher baseline GH/insulin-like growth factor-1 levels
- Tumour volume T4/T5
- Increasing tumour size

In conclusion, aggressive pituitary adenomas represent a distinct entity, with heterogeneity of cells, different biological and genetic characteristics, and new mutations.

FIPA, acromegaly and gigantism

Familial disease

Albert Beckers (Liège, Belgium) described recent data regarding familial isolated pituitary adenomas (FIPA). An international collaborative study performed across 36 centres in 14 countries compared 96 patients with *AIP* mutations with 232 patients who were negative for *AIP* mutations. A total of 43 separate mutations were found.

In patients with somatotrophinomas, those with *AIP* mutations were younger at first symptoms and at diagnosis, the tumours were larger and more invasive, disease control was less good and there were higher growth hormone (GH) levels at diagnosis. Somatostatin analogues (SSAs) were less effective in reducing GH levels and shrinking the tumours, and repeat operations were needed more often.

Some 211 families with FIPA have been identified: 127 homogeneous and 84 heterogeneous. Most adenomas with an *AIP* mutation (86%) secrete GH or prolactin. Most germline mutations are mis-sense, nonsense or small deletions, though large deletions have been observed. Exon 6 is the location of 48% of mutations. There are no obvious correlations between age at diagnosis and type of mutation, age at diagnosis and type of secretion, or mutation type and type of tumour.

At-risk groups for *AIP* mutations include gigantism (30%), FIPA (15–20%), children with pituitary adenoma (9–25%), and sporadic macroadenoma under the age of 30 (11%). FIPA can include all phenotypes; 20% of FIPA cases have *AIP* mutations but the aetiology is unknown in 80%.

Acromegaly and gigantism

Professor Beckers described findings from the Liège Acromegaly Survey, which includes 3200 patients from 15 different centres and analyses data from 1970 onwards.

Young patients have more aggressive tumours, but in recent decades milder disease is being diagnosed in older patients. The sex ratio varies between centres. As regards aetiology, 1619 sporadic and 50 familial cases have been identified, giving a 3% figure for familial causes. Glucose metabolism and red blood cell count correlate with insulin-like growth factor-1 (IGF-1) but not GH levels. Pretreatment with SSAs has risen decade by decade; results are better with pretreated patients. Debulking significantly reduces the IGF-1 level.

The clinical and genetic characteristics of patients with gigantism were also discussed. In a retrospective study using many centres worldwide, 231 tall patients were recruited (with a final height greater than 2 S.D. scores above normal for their population, or with abnormal, excessively rapid, growth velocity for their age). A total of 192 patients with pituitary gigantism were identified, 155 male and 37 female. From these, 25 cases of FIPA were found, and germline *AIP* gene mutations or deletions were found in one third.

Women were younger at diagnosis than men (16 versus 22 years) and the mean delay in diagnosis was 4.5 years. Most patients (96%) had acromegalic features at diagnosis. Most had large tumours: 86% had macroadenomas, 77% had extrasellar extension and 55% had invasive tumours.

In conclusion:

- Male gender is over-represented (82%)
- *AIP* mutations explain only 30% of gigantism; other genetic features are yet to be identified
- Pituitary adenomas are diagnosed earlier in females
- Treatment delay may increase the damage caused by GH excess
- Amelioration of most clinical symptoms on treatment is not satisfactory
- Pituitary tumours in general are large, even giant in 18%
- Somatotrophinomas are difficult to control; multimodal treatment is frequently required

10 years' clinical experience with pegvisomant

AJ van der Lely (Rotterdam, The Netherlands) discussed the lessons learned during 10 years of clinical experience with pegvisomant. Somavert was launched across Europe and the USA in 2003–2006, and the first patient was enrolled in ACROSTUDY in 2004. ACROSTUDY is a post-authorisation safety surveillance study of patients with acromegaly treated with pegvisomant, to monitor long-term safety and outcomes.

How well does pegvisomant work in everyday practice? When properly dosed, everybody will respond, he said, but some patients need more pegvisomant. Recent findings show that insulin-like growth factor-1 (IGF-1) is normalised in more than 90% of patients at 9 years, with a median dose of 80mg/week.⁶ Predictors of responsiveness to pegvisomant are male gender, radiotherapy, body weight and baseline IGF-1.

An 'escape' phenomenon has been discussed, such that over time patients gradually need more pegvisomant to control the IGF-1 level. Many patients have IGF-1 levels around the upper limit of normal (ULN), said Professor van der Lely; the escape phenomenon is more likely to be a dosing issue than true tachyphylaxis.

Which patients develop liver function disturbances?

In ACROSTUDY, about 3% of subjects show raised aspartate aminotransferase or alanine aminotransferase greater than three times ULN. Safety data up to 9 years are available for 141 patients in The Netherlands. Elevated transaminases were thought to be related to pegvisomant use in 19 patients (13.5%). Pegvisomant-induced liver injury appears to be related to the polymorphism of Gilbert's syndrome. The incidence of elevated liver function tests (LFTs) depends on the frequency of assessments. It is somewhat higher when pegvisomant is combined with somatostatin analogues (SSAs). No cases of liver failure or irreversible damage have been described to date.

In conclusion:

- The efficacy of pegvisomant is high in clinical practice, provided that proper dosing has been applied
- Normalisation of IGF-1 is possible in more than 95% of patients with a median dose of 80mg/week
- Increases in tumour size and raised LFTs do not seem to be a clinical problem
- Pegvisomant also works in patients who are resistant to SSAs

What are the real efficacy and safety of somatostatin analogue therapy?

The somatostatin analogues (SSAs) octreotide and lanreotide were reviewed by Mônica Gadelha (Rio de Janeiro, Brazil). SSA studies generally report response rates of about 50%, but results from three recently published prospective clinical trials have shown lower efficacy (17.3, 19.2 and 27.1%). SSAs have been used as the mainstay of medical therapy in the treatment of acromegaly for 30 years – what is their real biochemical efficacy?

To answer this question, PubMed was searched for English language studies evaluating acromegaly patients treated with octreotide or lanreotide between 1996 and January 2014. The response rates to octreotide varied from 17 to 86%, and to lanreotide Autogel® from 17 to 84%. How can these differences be explained?

The following are some factors that may have an impact on response rates:

- Standardisation of assays for growth hormone (GH) and insulin-like growth factor-1 (IGF-1) may be lacking
- Composite end points consistently result in lower response rates compared with GH or IGF-1 end points
- Different patient populations have different response rates. In particular, patients with previous SSA treatment have a higher (55%) response rate than medical treatment-naïve patients (17%)
- Retrospective analysis can bias the response rate
- Analysis of the ITT (intention-to-treat) population can lead to lower response rates than analysis of the per-protocol population

Professor Gadelha described a study of real-life SSA efficacy in a single centre, her university hospital. There were 150 patients, 65% of them female, with a mean age of 43.9 years. They were treated with octreotide LAR®, and 37.3% received this as primary treatment. Results achieved in these 150 patients were GH<1µg/l in 36.0%, normal IGF-1 in 36.7%, and GH<1µg/l and normal IGF-1 in 28.7%. Some 16.1% of patients with primary SSA treatment and 35.6% on adjuvant treatment

achieved GH <1µg/l and normal IGF-1 (P=0.011). Professor Gadelha concluded that the interpretation of biochemical response rates is critically dependent on the context of the study. Many factors may influence interpretation of the data, and different studies cannot be directly compared.

In the nine studies in which tumour shrinkage was quantified, octreotide LAR® treatment led to clinically relevant tumour shrinkage in more than 50% of patients. In one study of 244 patients published in 2014, mean tumour volume assessed by magnetic resonance imaging decreased from baseline by 40% in the pasireotide group and by 38% in the octreotide groups respectively, at 12 months.

What of the safety of the SSAs? A comprehensive review of safety in patients receiving octreotide revealed no major concerns.

Individualised medical therapy is the ideal for acromegaly. Suggested mechanisms and predictive factors for SSA resistance include: younger age, male gender, high GH, sparsely granulated tumours, high Ki-67, and low *sst2*, low *AIP* and high beta-arrestin1 expression. Assessment of *AIP* expression levels may represent a useful guide in the clinical decision-making process, for example.

In conclusion, SSA monotherapy has an important place in the medical treatment of acromegaly, with a biochemical efficacy of 30–40%, a significant decrease in tumour volume in more than 50% and a favourable safety profile. Treatment based on biomarkers will improve the percentage of controlled patients with a particular drug.

DEBATE: To debulk or not to debulk?

In the second Oxford-style debate, the case for debulking was put by Christian Strasburger (Berlin, Germany), while the case against was detailed by Michael Buchfelder (Erlangen, Germany). Debulking is an operative procedure in which the entire tumour cannot be removed and therefore is necessarily a surgical failure, commented Professor Buchfelder.

Background

What are the goals of therapy for pituitary tumours?

- To control growth hormone (GH) and insulin-like growth factor-1 (IGF-1) hypersecretion
- To reduce the morbidity and mortality related to uncontrolled GH secretion
- To reduce tumour volume
- To control local tumour mass effects
- To prevent disease recurrence

Knosp and colleagues classified parasellar invasion of pituitary tumours according to their extension in relation to the intracavernous carotid artery.⁷ Published data show that it is

not possible to obtain endocrine (GH and IGF-1) remission of acromegaly if the tumour diameter is greater than 40mm (compared with 89% remission for tumour diameter ≤10mm).

Opinions were invited from the audience at this stage: almost all agreed that an operation should still be the primary treatment for invasive macroadenomas, even if total tumour resection were definitely excluded.

Debulking in combination with SSAs

The treatment algorithm for acromegaly published in the 2009 guidelines recommends that surgery should be used for a pituitary tumour if a surgical cure is expected.⁸ If post-operative disease is expected to persist, then



somatostatin receptor ligands should be initiated if there are no signs of compression. Moreover, said Professor Buchfelder, surgery is not able to enhance the response to somatostatin analogues (SSAs); Newman's 1998 paper showed that GH was normalised in only 60% of patients who had surgery or radiotherapy before octreotide therapy, but in 75% of patients treated with octreotide alone.⁹

Patient selection bias explains the findings from the Newman study, argued Professor Strasburger. Actually there is evidence that surgery may enhance the response rate to SSAs. The 2005 study by Petrossians and colleagues showed that GH was normalised in 54% of patients and IGF-1 in 78% of patients who had SSAs after surgery (the respective percentages in patients who received SSAs before surgery were 29 and 46%).¹⁰ The authors concluded that gross total resection of tumours improves hormonal control of acromegaly by SSAs in patients whose adenomas were not amenable to complete surgical resection, and in whom primary SSA therapy was unable to achieve good biochemical control. Colao *et al.* also showed that partial surgical removal of GH-secreting pituitary tumours enhances the response to SSAs in acromegaly.¹¹

Professor Buchfelder commented that his colleague had not mentioned complications. According to the surgeon's caseload, between a quarter and a third of patients have complications from pituitary surgery, such as carotid artery injury, haemorrhage, permanent loss of vision, central nervous system injury and even death.

Predicting response to medical therapy

Professor Strasburger then addressed whether it is possible to predict a response to medical therapy with dopamine agonists and SSAs.

In quantitative analysis of somatostatin receptor subtype (SSTR1–5) gene expression levels in somatotrophinomas and non-functioning pituitary adenomas, SSTR5 was the dominant subtype in 52% of somatotrophinomas. In 39%, SSTR2 mRNA levels were dominant.

A positive correlation between SSTR2 levels and percentage decrease in GH was found after 3 and 6 months, and in IGF-1 after 6 months, after 6 months of octreotide LAR®. The percentage decrease in IGF-1 after a 3-month course of octreotide LAR® was negatively correlated to SSTR5 levels.¹²

Brzana and colleagues found that GH granulation pattern and SSTR2A correlate with post-operative somatostatin receptor ligand response in acromegaly.¹³ In this large single centre study, tumours from 59 patients were divided into densely granulated, sparsely granulated and mixed GH/prolactin. The densely granulated tumours all expressed SSTR2A, and 50% of the sparsely granulated tumours expressed SSTR2A. In SSTR2-positive tumours, an adequate response to therapy was obtained in 81% of cases; none of the SSTR2-negative tumours responded.

It is also useful to know whether dopamine receptors are present in the tumour, since this implies that cabergoline may normalise the IGF-1 level, even in patients who are resistant to long term treatment with SSAs. Professor Strasburger concluded by saying that debulking provides the clinician with tumour tissue, which enables him to start tailoring therapy for the individual patient.

When delegates were asked to vote again on whether they were in favour of debulking, practically everybody was in favour of the procedure.

History of acromegaly

In his review of the history of the disease, Wouter de Herder (Rotterdam, The Netherlands) commended Dr Leonard P Mark's book *Acromegaly: a Personal Experience* (Baillière Tindall & Cox, London, 1912), which is a record of a doctor's personal experience of acromegaly.



Potential new biomarkers

The search for potential new biomarkers in acromegaly was described by Jens Otto Jørgensen (Aarhus, Denmark). New biomarkers may be sought in aspects of tumour morphology (such as T2-weighted magnetic resonance imaging), growth hormone (GH) signalling pathways, GH-induced gene expression and identification of proteins in the circulation.

Professor Jørgensen presented a paper examining gene expression in skeletal muscle after an acute intravenous GH bolus in humans; the authors identified a mechanism regulating angiopoietin-like 4 (ANGPTL4).¹⁴ Muscle biopsies were performed after GH injection, and 79 acute GH-responsive genes were identified in skeletal muscle. Their functions include cellular development, cellular growth and proliferation and amino acid/carbohydrate/lipid metabolism, and all 79 are potential new biomarkers. *CISH* and *SOCS1–3* gene expression (involved in JAK-STAT signalling) were directly induced by GH.

ANGPTL4 is involved in lipolysis and suppression of lipoprotein lipase activity, and it was a surprise that it was regulated by GH, said Professor Jørgensen. The GH-induced increase in ANGPTL4 expression appears to be linked to the observed concomitant increase in serum free fatty acid levels. In a study that compared ANGPTL4 expression in patients 'cured' by surgery or somatostatin analogues (SSAs), there was a positive correlation between serum non-esterified fatty acids and ANGPTL4 expression in skeletal muscle.

Another approach is to measure biomarkers in interstitial fluid to estimate disease activity in target organs. No difference was found between bioactive insulin-like growth factor-1 (IGF-1) in suction blisters from patients with acromegaly who had been 'cured' with surgery or SSAs (unpublished data).

Serum proteomics using 2D gel provides a further approach to looking at differences in protein levels, identifying them and evaluating their potential as novel biomarkers. A serum sample is taken and manipulated in one dimension with isoelectric focusing and in a second dimension with SDS-PAGE. Spots of interest are identified using mass spectrometry.

One study examined samples from patients with acromegaly before and after successful treatment by surgery, as shown by post-operative reductions in GH and IGF-1. Seven spots were identified on 2D serum gel: levels of six proteins (including transthyretin, haptoglobin, apolipoprotein A-I and β -haemoglobin) fell after surgery and the level of complement C4B precursor rose after surgery (indicating that GH suppresses this last protein). At times, GH regulation changes the isoform of the protein rather than the total protein level.

In conclusion:

- GH signalling in human target tissues *in vivo* is a promising investigational model
- GH-induced gene expression may provide a pool of biomarkers in health and disease
- Proteomics may disclose novel humoral biomarkers, but more research is needed.

Breakout discussion III

Stem cell therapy

During discussion at the third breakout session, delegates were asked whether they believed that stem cell therapy would have a place in clinical neuroendocrinology. All groups believed that this might be an interesting option, but not in the near future. One group commented that the presence of pituitary stem cells that can give rise to all pituitary cell types implies that these critical stem cells can be replaced after loss or damage. Replacement therapy remains challenging for all hormones, as peripheral hormones do not mimic ideally the physiological secretion of each endocrine organ. There are potential side effects and it would be a very expensive option. It was also pointed out that stem cell replacement could be useful in terms of patient compliance.

Biomarkers

The groups' opinions were also sought on whether we need new biomarkers for active acromegaly. In Group C, 90%

thought that growth hormone (GH) and insulin-like growth factor-1 (IGF-1) alone were sufficient, but they also pointed out that symptoms and other metabolic parameters such as glucose should be monitored, along with quality of life.

Group D wanted biomarkers to monitor disease activity and effectiveness of treatment. Group A concurred, pointing out that although GH and IGF-1 concentrations are important biochemical parameters for diagnosis and follow-up of acromegaly, their serum measurement does not reflect the tissue concentration of these hormones. They called for new markers to define active acromegaly.

Stable biomarkers to reflect GH control over long time periods would be useful, said Group B, analogous to monitoring HbA1c (glycated haemoglobin) in diabetes. They also called for new pathological biomarkers for pituitary tumour tissue, preferably measurable in blood.

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Pfizer Inc. was the sole sponsor of the 5th Annual European Meeting on the Management of Acromegaly and the programme was developed by a Scientific Planning Committee (SPC). The SPC comprises specialists who provide scientific and planning oversight for the overall programme and content. Its members are recognised authorities in the field of endocrinology, and they receive an honorarium from Pfizer Inc. for this

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