Dear Conference Delegate,

A warm welcome to all attending the conference on “Advances in diagnosis and treatment of growth disorders”. I would like to inform you that as of 28 April 2014 the name of our Foundation changed to EXCEMED – Excellence in Medical Education. The name change will not impact your registration status in this or any other Foundation event.

This transition marks an exciting point in the evolution of the Foundation. We are proud to have provided world-class education to thousands of healthcare professionals over the past four decades - as a result, the Foundation has become synonymous with delivery excellence and high-impact CME.

As we further develop our scientific and geographical presence it is important to us that our name accurately reflects the independent nature of the education we provide; EXCEMED symbolises our enduring mission to support the best possible outcomes for patients through the medical education we offer. We take pride in our complete dedication to the provision of CME - it is our sole focus and our passion.

I wish you an inspiring and successful learning experience here in Istanbul.

Yours sincerely,

Rachel Clark
CEO, EXCEMED
General information

Venue
This live educational conference takes place at the:

Elite World Prestij Hotel
Şehit Muhtar Caddesi No:40
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Language
The official language of this live educational conference is English.

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Advances in diagnosis and treatment of growth disorders

EXCEMED live educational conference on:

Advances in diagnosis and treatment of growth disorders
10 May 2014 - Istanbul, Turkey

Background and aims
Growth disorders are a common problem around the globe, frequently resulting from genetic predisposition and environmental factors such as malnutrition or secondary diseases in some regions. Screening, diagnosis and management of conditions such as short stature, puberty delay, and lower adult height, are significant challenges for healthcare professionals because of the lack of diagnosis and treatment guidelines and insufficient focus on relevant medical education. EXCEMED is continuing its mission to disseminate the latest knowledge and achievements in the field of growth disorders by organising a conference in 2014 designed for paediatric endocrinologists and scientists dealing with these conditions. This conference will be led by international experts in the field and will include discussion of the most important advances in research and clinical settings, and provide an opportunity to share best practice in managing such diseases in daily practice.

Learning objectives
By attending this live educational conference, learners will have up-to-date knowledge about the latest developments in research and clinical management of growth disorders, and particularly will be able to:
• Recognise the burden of growth disorders in the paediatric community
• Enhance their diagnostic and therapeutic approaches with the use of approved guidelines
• Improve the use of growth hormone therapy in the light of pharmacogenomic evidence and the long-term effects of such treatment
• Describe the use of growth hormone therapy in different conditions and comorbidities
• Discuss tools for achieving better treatment adherence

Target audience
Pediatric endocrinologists, scientists, and all the professionals involved in managing children with growth disorders.
Accreditation

EXCEMED [www.excemed.org] is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The CME conference on: “Advances in diagnosis and treatment of growth disorders” held on 10 May 2014 in Istanbul, Turkey, is designated for a maximum of 6 (six) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.

EXCEMED adheres to the principles of the Good CME Practice Group (gCMEp)

We value your opinion!
We are continually trying to develop and improve our educational initiatives to provide you with cutting-edge learning activities. During this conference you will be asked to answer a real-time survey and after this educational event you will be receiving an online survey to help to better tailor our future educational initiatives.

We thank you for participating!

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Saturday, 10 May 2014

8.45 Welcome and introduction
Martin Savage [UK]

Session I Growth disorders, diagnosis and effects
Chairman: Martin Savage [UK]
Real time survey
9.00 L1: Guidelines for achieving a correct diagnosis in the child with short stature
Stefano Cianfarani [Italy]
9.30 L2: Next-generation sequencing for uncovering novel genetic causes of short stature
Jan-Maarten Wit [Netherlands]
10.00 L3: Psychological distress in children with growth deficits
John Chaplin [Sweden]
10.30 Revisiting real time survey
Q&A
10.45 Coffee break

Session II New perspectives in managing growth disorders
Chairman: Pierre Chatelain [France]
Real time survey
11.00 L4: Addressing puberty delay in growth disorders
Abdullah Bereket [Turkey]
11.30 L5: Achieving optimal adult height from GH therapy
Michael B. Ranke [Germany]
12.00 L6: A balanced view of the management of idiopathic short stature
Martin Savage [UK]
12.30 Revisiting real time survey
Q&A
12.45 Lunch

Session III Interactive workshops with clinical case presentations
Chairman: Stefano Cianfarani [Italy] - Pierre Chatelain, France
Real time survey
14.00 CC1: Management and GH treatment in small for gestational age patients
Valentina Pampanini [Italy]
14.45 Discussion
15.00 CC2: GH therapy in Turner syndrome patients
Marco Cappa [Italy]
15.45 Discussion
Revisiting real time survey
16.00 Coffee break

Session IV Improving treatment in growth disorders
Chairman: Abdullah Bereket [Turkey]
Real time survey
16.30 L7: The PREDICT study: applying pharmacogenomics to growth disorders
Pierre Chatelain [France]
17.00 L8: Transitional age and GH treatment
Stephen Shalet [UK]
17.30 L9: The problem of adherence to treatment in growth disorders
Svante Norgren [Sweden]
18.00 Revisiting real time survey
Q&A
18.15 Closing remarks - Conclusions
Pierre Chatelain [France] - Martin Savage [UK]
18.30 End of the live educational conference

Legend: L: Lecture; CC: Clinical Cases
Abstracts
Statistically, short stature is defined as a length/height <-2.0 SDS for age, sex and pubertal stage of the appropriate reference population. GH and IGF-I are essential for regulating growth.

There is a continuum of defects in the GH–IGF axis in individuals with short stature that ranges from GHD through ISS to severe primary IGFD - the short stature continuum. GH stimulation tests are burdened with a high rate of false positive results. A value of IGF-I and IGFBP-3 in the (low) normal range does not exclude GHD, however IGF-I levels > 0 SDS are strongly against GHD. IGF-I & IGFBP-3 values < -1.9 SDS strongly suggest GHD. Normal GH values + low IGF-I & IGFBP-3 levels ➔ neurosecretory dysfunction or GH receptor deficiency. To achieve the correct diagnosis of short stature a comprehensive approach (clinical, anthropometric, biochemical, endocrine, neuroradiological and genetic) is necessary. Establishing the genotype can aid the management of individual patients with hypopituitarism. For example, in a patient with an identified PROP1 mutation careful monitoring of the anterior pituitary is indicated. The identification of a mutation within POU1F1 predicts that cortisol and gonadotrophin secretion will remain normal in the patient. Identification of the genotype can also aid in genetic counseling and early diagnosis.

A genetic etiology include the:
* Early onset of growth failure.
* A positive family history.
* Consanguinity.
* Severe growth failure [height SDS < -3]
* Extremely low growth hormone response to a provocation tests.
* Very low insulin-like growth factor 1 [IGF-1] levels.
Background
In many patients with pediatric endocrine disorders routine diagnostic procedures, including targeted genetic tests and whole genome SNP-arrays, do not lead to a definite diagnosis. Next-generation sequencing, currently mainly whole exome sequencing (WES), is rapidly becoming available in many laboratories, and has already revealed many novel genetic defects. WES will probably soon be replaced by whole genome sequencing. Requirements for WES include a proper facility for exome capturing and sequencing; sequencing with sufficient coverage; and an efficient pipeline for downstream analysis.

Objective
To illustrate the usefulness of whole exome sequencing, five cases will be presented.

Results
WES was performed on DNA samples from 7 families, and led to a diagnosis in five. In two cousins with central hypothyroidism an IGF1 mutation was found, and subsequently 10 other families with different mutations in the same gene were discovered [Sun et al., 2012; Joustra et al., 2013]. In a male giant (221 cm) an activating mutation in NPR2 was detected [Hannema et al., 2013]. In a family with dominant proportionate short stature, we discovered a novel mutation in FGFR3 (p.Met528Ile), close to the position affected in hypochondroplasia (p.Asn540Lys) [Kant et al., submitted]. In two brothers with disproportionate short stature, skeletal deformities and low serum DHEAS, a novel compound heterozygous mutation was found in PAPSS2 [Oostdijk et al., in preparation]. A girl with severe obesity, in whom genetic tests were said to have been negative, showed compound heterozygosity for two LEPR (leptin receptor) mutations [Hannema et al., in preparation]. All mutations were confirmed with Sanger sequencing, and in three cases functional studies were done.

Conclusion
NGS is a powerful technique to solve diagnostic problems if a genetic cause is suspected.
Psychological distress can manifest in multiple ways and at different levels of severity. In general terms psychological distress condition leading to an impact on the functioning of the individual. It can be experienced as anxiety, anger, depression and in the most extreme cases can result in suicide. In cases of short stature, mild psychological distress might be caused by everyday stressors such as the inability to reach things or purchase clothes in the right size whereas severe distress can be caused by extreme or prolonged stressors such as persistent bullying. Since no two people experience one event in exactly the same way, psychological distress is a subjective experience. The severity of psychological distress is therefore, dependent upon the situation and how it is perceived by the individual. In this presentation I will review the evidence for the existence of psychological distress through the recent literature concerning short stature and suicide and poor quality of life. I will also review the evidence for the determinants of psychological distress such as bullying, poor self-evaluation and juvenilisation.
In addition to many changes in the body, pubertal period is characterised by acceleration of linear growth with height velocity reaching up to 8-12 cm/year during “pubertal spurt”. Approximately 15--30 cms of height of an individual is accrued during puberty. Thus, normal timing and tempo of puberty is a prerequisite for reaching full height potential. Estrogen is the principal hormone stimulating the pubertal growth spurt in both sexes. This action is mediated through ERa and ERb receptors in the human growth plate. In addition, sex steroids have important effects on the GH-IGF axis as evidenced by diminished endogeneous GH secretion by estrogen receptor blocking.

Delayed puberty can simply be defined as no testicular enlargement by age 14 in boys and no breast development by age 13 in girls and, depending on the etiology, can be transient, reversible or permanent. Constitutional delay in growth and puberty is the most likely scenario in a a short child with delayed puberty, however this is a diagnosis of exclusion and should be established after exclusion of more serious conditions such as hypopituitarism, Turner Syndrome etc. Basal and/or GnRH stimulated gonadotropin levels, T/E2, karyotype in hypergonadotropic situations usually suffice in excluding these conditions.

Optimal management of pubertal delay requires timely initiation and fine tuning of sex steroid treatment so as to mimick normal physiology as much as possible which is a challenging task. It is not possible to give evidence-based guidelines in this matter since in most cases, the decision must be based on the etiology of delayed puberty and other individual factors such as height, bone age etc. In conditions where height prognosis is poor [such as in Turner Syndrome] pubertal induction may be postponed a while until achievement of an “acceptable” height. In boys with constitutional delay in growth and puberty, the benefits of T replacement therapy may include accelerating growth rate, inducing pubertal onset, improve psychosocial function, and assures normal bone mineral accretion during the critical period of adolescence and improves muscle mass and strength, but it shortens pubertal duration with apparently no adverse effect on final adult Ht. Nonaromatisable androgen [oxandrolone] may result in a bettter height prognosis but evidence is weak and the drug is not available in many countries.
The spectrum of approved indications for GH has expanded from GHD to Turner syndrome, SGA, Cri, Prader-Willi syndrome, and ISS. However, even in GHD only about 80% of the children achieve an adult height within the normal range. This is partly the consequence of an inflexible treatment modality, which is guided by historical developments, uncertainty about the aims of treatment, imprecise diagnoses, inappropriate dosing of GH, lack of patients’ adherence, limited knowledge of physicians about rare disorders and a wait-and-see attitude. In order to reach modern treatment goals and to avoid unnecessary, potentially harmful and extremely expensive therapies in short children GH treatment needs to be optimised and individualised.

The aims of the current discussion are a) to discuss the aspects potentially impairing an optimal height development and b) to argue that GH treatment should be guided by the responsiveness to GH rather than by exclusively considering the response. – ad b): Since it is impossible to determine a dose-response curve of a treated individual one needs to deduce the individual responsiveness by comparison of the observed response with the expected most likely response of the patients. This means to determine the relative responsiveness in relationship to a group with the same diagnosis. The most likely response (for a diagnosis and a period of treatment) can be calculated with the help of algorithms [prediction models] which are derived by means of regression analysis taking into consideration the various characteristics of a group of patients. Short-term responsiveness is a major predictor of adult height development.

Currently, the models allow to develop realistic ideas about the short- and long-term growth potential of individual children. Deviations of observed from expected growth can help to identify their causes such as non-compliance (adherence), additional disease, and impaired responsiveness. Optimizing the long-term outcomes with regard to the amount of GH (costs) is another potential of the use of prediction models, since highly responsive individuals may need less - and less responsive individuals may need more (or no) GH. Thus, the use of prediction models will become routine in the quest to optimise GH treatment.
Management of idiopathic short stature (ISS) is a controversial topic because some clinicians favour therapy with GH in most ISS patients, whereas others are much more conservative and interpret GH therapy in this context as interference. The truth lies somewhere between these extremes. ISS is defined as short stature (height < -2 SD) associated with normal birth weight, absence of chromosomal defects or dysmorphic features or chronic disease and normal GH secretion. Therapeutic trials using rhGH mostly performed in the USA in the 1980s and 1990s showed increased short-term growth compared with placebo- or un-treated control groups and a good safety record. These data were submitted to the FDA and in 2003 ISS became an approved indication for GH therapy in the USA. Since then, many thousands of ISS patients have been treated. However similar applications have been submitted to the EMA and approval has not been granted, due largely to the opinion that clinical benefit due to increase in adult height has not been sufficiently demonstrated. The long-term results of GH therapy in ISS are relatively disappointing with a mean increase of 3-5 cm compared with untreated controls. Predictors of good response are severity of short stature, young age at onset of therapy and tall parents. Many children however start therapy late, ie at ~10 years and have short parents. These patients consequently have a relatively poor response rate, estimated at 35-40%. Treatment if therefore controversial and the pros and cons will be debated in this presentation.
Objective
To provide insights into underlying etiologies responsible for short stature in SGA children and highlight aspects of therapeutic management in this patients.

Topic
I will present a clinical case of a SGA child who referred to our outpatient clinic for severe growth retardation. The severity of short stature together with the presence of dysmorphic features and relatively high IGF-I levels, prompted to extend diagnostic assessments to genetic testing. Karyotype and array CGH unravelled the presence of a ring chromosome 15, a genetic abnormality involving IGF-IR gene. RhGH treatment was started according to EMEA indications and discontinued after one year for inadequate growth response.

Critical Issues

Conclusions
Early evaluation of short children born SGA is recommended and should consist of assessment of the GH-IGF-I axis when signs of GH deficiency are present. Genetic abnormalities of GH-IGF-I axis, such as IGF-I or IGF-I receptor point mutation, deletions and polymorphism, can be responsible for small size at birth and persistent short stature. Their identification allows to identify the cause of short stature and to have interesting insights about rhGH therapy response. Discontinuation of rhGH treatment should be considered according to growth response.

Acronyms
rhGH-recombinant human growth hormone, SGA-small for gestational age, EMEA-European Agency for the Evaluation of Medicinal Products.
Turner syndrome (TS) occurs in one in 2500 live-born females and is associated with specific characteristic features. One the most common features is short stature and a mean adult height is between -2.0 -3.0 SD as shown in national and international studies. SHOX haploinsufficiency due to the lack of a sex chromosome is considered to be the main cause of short stature in individuals with Turner syndrome. Many studies have demonstrated the effect of GH therapy on height in patients with TS and in SHOX deficiency (SHOXD) patients because of the similar etiology. There have been marked advances in the treatment of both TS and SHOXD, early interventions with growth hormone and hormonal replacement therapy seems to clearly improve the Turner syndromes final height of about 6 cm. Specific studies, in TS, estimated that 0.7-1.2 SD are lost before birth and 1.3-1.8 SD are lost in the first 3 year of life, suggesting that GH treatment should be proposed early at least before 4 years. At the presumed onset of puberty associated treatment with Oxandrolone or low dose of Estrogen will further improve the outcome in TS.
Abstract not in hand at the time of printing.
The development of osteoporosis, with its attendant risk of fragility fracture, is in part related to the PBM achieved in early adulthood. Adolescence is a crucial time for the acquisition of bone mass; during pubertal maturation, areal bone mineral content (BMC) and bone mineral density (BMD) at the lumbar spine and femur increase by 4- to 6-fold over 3 years (11-14 in girls and 13-16 in boys), such that approximately 37% of skeletal mass is accrued between pubertal stages 2 and 5. Bone mineral accretion continues after this time, although the precise timing of the attainment of PBM is not certain and varies between skeletal sites. Areal BMD at the femur peaks around the age of 20 years whereas maximum total skeletal mass occurs 6-10 years later.

There is now increasing evidence that the skeletal impact of, and immediate requirement for GH, in a severely GHD teenager after final height, is dependent partly upon the degree of optimisation of GH replacement during childhood; the greater the margin by which a GHD child fails to achieve target height at cessation of growth, the less total bone mineral content (BMC - height corrected) is accrued.

In severely GHD teenagers [mean age 19 yrs; IGF-I less than 1st centile for age] however, bone mass increases by approximately 5% over 2 years despite remaining off GH and the two year gain in bone mass is inversely correlated with the length of time since the last pediatric GH injection. In those severely GHD teenagers in whom GH is replaced over the same 2 year period the gain in bone mass is approximately 10% and the first year increment is related inversely to the time since the last pediatric GH injection.

Thus these data suggest that seamless transition of GH therapy is preferable to allowing a gap in GH therapy to exist for a few years. The skeletal treatment effect does not appear dose-dependent within the range 12.5-25 micrograms/kg/day for teenagers of 19 years of age but may be so for older individuals [24 years].

The window of opportunity concept will continue to be challenged by GHD teenagers who will not consent to seamless continuation of GH replacement from early childhood through to young adult life (25 years) without a break.
Improving adherence to treatment may have greater impact on treatment outcome and patient safety than improvements in specific medical treatments. There is accumulating data suggesting that adherence is a significant problem and limits the response to growth hormone treatment. Poor adherence may result from either practical barriers or motivational barriers causing doubts about the necessity of medication or concerns about potential side effects. Forming an alliance with the parents and the patients and addressing these barriers are key issues in order to improve adherence and treatment outcome.
Disclosure of faculty relationships

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