GH TREATMENT OF NON GROWTH HORMONE DEFICIENT SHORT STATURE

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The term non GH deficient short stature is a vague term that paediatric endocrinologist are using to "define " a population of short children without evidence of a precise cause or mechanism and certainly no known endocrine cause. We will consider in this presentation 2 entities that have received a lot of attention from both side of the Atlantic namely the child born Short for Gestational Age and the child with Idiopathic Short Stature. A 3d situation will be considered at the end : the case of corticoid induced growth retardation in chronic inflammatory diseases and the role of GH administration to treat or prevent the severe short stature frequently observed in these children.

SHORT CHILDREN BORN SHORT FOR GESTATIONAL AGE (SGA)

According to the most widely used definition 3% of neonates are born SGA either because their birth weight or length are 2 SD below the mean for gestational age and background population. These children experience a rapid catch up but about 10% of them will remain short and will be short as adult. In a population study performed in France we have compared a group of adult born SGA to a control group and we have shown that the adult height of the SGA group is 1 SD below the control and that 10% of them are 2SD below the mean.

Several studies have shown that administration of GH to short children born SGA can increase the growth velocity (GV) of these children but more importantly, a long term study performed in Europe has shown that GH can normalize the adult height and avoid short stature. An international consensus meeting has clearly defined the objective of treatment: to induce a rapid catch up to normal height, to maintain a normal height during childhood and to reach a normal height as adult. It seems reasonable to start treatment after the age of 3 when it is certain that no catch will occur and to treat the shorter children. There is a controversy about the best GH dosage to be used in this indication. If a "low" GH dosage of 33ùg/Kg/Day seems to be able to normalize adult height in the less severe form, we recommend using a larger dosage in the early years of treatment to allow a rapid catch up. A larger dosage (between 50 and 66 ùg) is also recommended in the most severe form of short stature (for example below -3 SD and in the prematurely born SGA children). GH administration seems to have other beneficial effects in these patients. In particular careful studies of body composition have shown that GH increases the lean mass in children born SGA and may correct the muscle mass deficit which has been described in this situation. Because children born SGA have some degree of insulin resistance and since GH administration by itself decreases insulin sensitivity, it was important to study glucose tolerance in this group of patients. Results are reassuring and during treatment as well as 6 years after resuming GH treatment no cases of diabetes have been observed and glucose tolerance is normal. Because the GH dosage induces an increase of plasma IGF-1 above the normal value for age, the question of a possible oncogenic risk remains open. Although the incidence of tumour in the treated group of patient is identical to what is expected, it seems important to maintain the IGF-1 plasma value below +2.5 SD and therefore measure this parameter at regular intervals. No new safety signals have been seen in the surveillance of large group of patient. Nevertheless since this is a new indication it seems important to continue some kind of surveillance in post marketing studies.

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IDIOPATHIC SHORT STATURE

A group of very short children with no precise phenotype or mechanism to explain their abnormal growth are classified as having idiopathic short stature (ISS). These children have marked growth retardation and achieve adult heights below their target height. Several studies have shown that long-term GH administration in children with ISS increases final adult height. These studies include randomised clinical trials and large surveillance studies, such as the National

Cooperative Growth Study (NCGS). The efficacy and safety of GH treatment in ISS is comparable to that observed in other non-GH deficient conditions. A consensus has not yet been reached on the best strategy to adopt for treating children with ISS. We recommend treating children with the most severe short stature (with a height limit d" -2.5 SD), starting at e"5 years of age. The patient's predicted adult height should be 1 SD below target height, as this will exclude children with familial short stature. Approximately 10-20% of children with ISS do not respond to GH treatment. Therefore, if growth velocity or the gain in height is not satisfactory after one year GH therapy should be stopped and the patient re-evaluated.

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SHORT STATURE IN CHILDREN INFLAMMATORY CHRONIC DISEASE AND TREATED WITH CORTICOID

Despite great efforts to develop alternative therapies, GC are still widely used and remain the first-line medication in the treatment of many chronic inflammatory and auto-immune diseases and in post-transplant recipients. In these pathological conditions, GC are usely given as a long–term treatment. Therefore, efforts should be done to reduce their adverse effects mainly affecting linear growth, muscle mass and bone health.

Paediatricians prescribing GC are well aware that minimal doses of GC should be given in order to minimize side-effects. For example, using other disease modifying or immuno-suppressive drugs can be a therapeutical option to decrease GC doses or to switch from a daily GC administration to an alternate day regimen. However, reducing GC doses without compromising the good control of the disease often remains a difficult challenge to achieve, particularly in severe inflammatory diseases. Since several years, observational and controlled studies assessed in children suffering from juvenile idiopathic arthritis (JIA) have shown that recombinant growth hormone(GH) therapy can halt the decrease in height velocity and muscle wasting that occurred during GC administration and can also improve bone mineralisation. However, responses to treatment markedly varied among the patients, depending on the severity of the underlying disease. In addition, the duration of the exposure to GC might also influence the response to GH treatment, through its deleterious effects on the growth plate and bone metabolism. Thus, starting GH treatment, later in the course of the disease, after many years of inflammation and GC exposure, in severely growth–retarded JIA children, would probably not lead to the normalization of their adult height and body composition although some moderate improvement has been observed in polyarticular forms of JIA treated until adult height. These observations incited us to initiate GH treatment in JIA patients earlier in the course of their disease in order to prevent rather than to cure these severe consequences of long-term GC therapy. Our results are convincing and we have shown that by initiating GH treatment early in the course of the disease (and of GC administration) it is possible to maintain a normal growth velocity and prevent short stature.

Glucose tolerance was studied during all these studies and surprisingly although insuline resistance was amplified by GH administration no cases of diabetes were observed.

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