Editorials

Who needs growth hormone?

Between 1958 and 1985, growth hormone (GH) was only available in limited supply from pituitary extract derived from human cadavers. Its use was retricted to children who had been demonstrated to be GH deficient in that they failed to achieve an (arbitrary) peak GH response of >7 mU/l to standard provocation tests, e.g. insulin induced hypoglycaemia or clonidine. Pituitary GH was withdrawn after concerns about the transmission of Creutzfeldt-Jakob disease[1-3]. Since 1985, biosynthetic growth hormone (produced by recombinant DNA technology) has been available in increasing amounts and is now available in quantities limited only by cost.

Potential metabolic side effects, which could include hypertension, glucose intolerance, and hyperlipidaemia seem not to be problematic in the medium term but all treated children must have close long-term supervision. Leukaemia may be more common in growth hormone deficient children treated with GH, but there is no evidence causally linking GH treatment with leukaemia.

Growth hormone needs to be given by daily subcutaneous injection (better growth is achieved with daily injections than with less frequent dosage). Doses of 20 iu/m^2/week are reasonable for prepubertal children but the optimal dose, particularly during puberty, remains unclear in many groups of patients.

This leads to some obvious questions: How should we define adequacy or inadequacy of GH secretory ability? Should its use still be limited to GH 'deficient' children? Are there other groups of children who could safely benefit from treatment, such as those with non-endocrine pathologies causing short stature, and short 'normal' children? You do not necessarily need underlying pathology to suffer as a result of short stature. Treatment goals need to be considered in broader psychological terms and not simply centimetres gained and final height[4].

Children can grow slowly for many reasons: poor growth is a 'final common pathway' for many organic and emotional problems of childhood[5]. Some pathological causes of poor growth should be relatively easy to determine, e.g. renal disease, malabsorbtion states, poorly-controlled asthma. Turner syndrome must be considered in all short or slowly growing girls, even if there are no dysmorphic features, and a karyotype performed. Other causes of poor growth can be very difficult to elucidate, e.g. emotional or other abuse, especially in apparently caring families. Growth in these circumstances will improve without growth hormone if the correct underlying diagnosis is found[6].

If a child is short or growing slowly and other pathologies have been reasonably excluded, tests of GH secretory ability should be performed. However, most are potentially dangerous[7] and can be difficult to interpret: the time of the last spontaneous pulse is unknown and will influence responsiveness, there is complex heterogeneity of circulating GH forms and GH assay variability and non-specificity, inadequate GH secretion may be physiological or secondary to other pathology and some short, slowly-growing children have an abnormal pattern of GH pulsatile release but normal responses to pharmacological tests 'neurosecretory dysfunction'. For these reasons GH provocation tests should only be performed in specialist centres[7].

There is a continuum of growth hormone secretory ability from children with severe GH insufficiency (GH 'deficiency'), through moderate GH insufficiency, through normal short (3rd centile), average height (50th centile) to normal tall (97th centile) individuals: Normal short children secrete less GH than their taller peers[8] and there is a non-linear relationship between the amount of GH secreted overnight and height velocity[9]. On a research basis, overnight GH profiles may given an indication of where on the spectrum of GH secretory ability a child lies: most normal children will produce three to four pulses of GH during the night with pulse amplitude >15-20 mU/l. Abnormal patterns of GH secretion can lead to poor growth. Nevertheless, accurate measurement of the child remains the most important screening 'diagnostic test'.

Children with 'classical' GH deficiency (or more accurately severe GH insufficiency) grow slowly and produce little GH spontaneously or in response to provocation tests. This may be due to poor pituitary somatotroph function or diminished secretion of GH releasing factor (GRF) from the hypothalamus. Severe GH insufficiency can be congenital or acquired. If congenital, it may be part of panhypopituitarism and so be suspected in the newborn period (hypoglycaemia, prolonged neonatal jaundice, micropenis) or be associated with other abnormalities, e.g. septo-optic dysplasia. Growth failure can then be anticipated and treatment started early. Early treatment with GH may also be important because of its metabolic effects, e.g. prevention of hypoglycaemia. If GH deficiency seems to be acquired, craniopharyngioma must always be considered: a child becoming blind from such a tumour is a preventable disaster.

An increasing number of children are now surviving childhood malignancies. Those that have received cranial irradiation (e.g. for brain tumours or acute lymphoblastic leukaemia) should have their growth carefully documented as severe growth hormone insufficiency is a common result[10-12]. This may largely be due to the effects of irradiation on the hypothalamus (affecting GRF secretion) as this may be more radiosensitive than the pituitary. Children surviving such malignancies long term deserve a good quality of life. Short stature in this situation is a preventable handicap and poor growth should be treated with GH once the prospect for long-term survival is good. In addition to GH they may also require other replacement therapy, e.g. thyroxine, corticosteroids. There is no evidence of a causal connection between GH therapy and an increased risk of leukaemia nor of tumour recurrence[13].

It is readily apparent that GH secretion will improve the growth of children who have severe GH insufficiency[14] provided there is no undue diagnostic delay and treatment is started early. Does GH therapy improve the growth of children who are producing more GH on the continuum of GH secretory ability, i.e. the 'short normal child'? Children in this situation can be short because they have (normal) short parents or because of significant growth delay (with potential or actual pubertal delay). The latter, if left untreated will eventually reach a 'normal' final height. Does GH improve the growth of the 'short normal child' in the short term only or will it lead to an eventual increase in adult height? Boys who have maturational delay will go through puberty later than their peers and their growth spurt will be significantly delayed. In this situation anabolic steroids[15] or low dose testosterone[16] may be cheaper, pleasanter and equally effective therapies. However, only prospective placebo-controlled studies to achieved (rather than predicted) final height will answer questions about the effect of GH and other growth-promoting therapies on, for example, age of pubertal onset, rate of pubertal progression and, thus, on final height.

Children in these circumstances are at one end of a spectrum of normality: why consider treating them with GH? The emotional and social consequences of short stature are not necessarily dependent on having underlying pathology, and many short children may not be normal in how they function emotionally[4]. They can be teased and bullied at school, and expectations are often based on physical size rather than chronological age. Many behave immaturely, aggressively, or under achieve. If combined with short stature, pubertal delay can add to the misery of young adolescents[17]. Thus, it is important to determine scientifically both effects on short- and long-term growth and whether growth-promoting treatments can significantly improve psychological well-being and performance before we can justify treating these 'normal' individuals. The psychological benefits of improving height velocity in the short to medium term could be important, even if final height is not significantly increased. Both growth and psychological evaluation until adult height is achieved will be important in answering these questions and such studies are in progress[18-20]. Emotional support may be just as, or more, important than growth promoting therapy. Treatment must be safe and long-term follow-up is required.

Growth hormone therapy is expensive, currently around £5000-£10 000 per annum per child. The demonstration of benefit in children with other than 'classical' GH deficiency or Turner syndrome (for the treatment of whom a product licence is available) must await the results of current trials, which are on-going, in children with skeletal dysplasias, intrauterine growth retardation, chronic renal failure, Noonan syndrome, familial short stature and constitutional delay of growth and puberty. GH therapy is not a substitute for explanation and psychological support, and parents and children must not be given unrealistic expectations of its effects on final height which may be slight in such patients.

Growth hormone currently has a product licence for use in 'GH deficiency' and Turner syndrome. Other groups of children are benefiting from treatment in the short to medium term, but long-term growth (to final height) and psychological studies are necessary before the place of GH in the treatment of these children is established. Meanwhile, GH must not be used indiscriminately.

Heather F Stirling
Christopher J H Kelnar
Department of Child Life and Health
17 Hatton Place, Edinburgh EH9 1UW, Scotland, UK

References

1 Powell-Jackson J, Kennedy P, Whitcombe EM, Weller RO, Preece MA, Newsom-Davis J. Creutzfeldt-Jakob disease after administration of human growth hormone. *Lancet* 1985;**2**:244-6
2 Koch TK, Berg BO, De Armond SJ, Gravina RF. Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism. *N Engl J Med* 1985;**313**:731-3
3 Ellis CJ, Katifi H, Weller RO. A further British case of growth hormone induced Creutzfeldt-Jacob disease. *J Neurol Neurosurg Psychiatry* 1992;**55**:1200-2
4 Kelnar CJH. Pride and prejudice - stature in perspective. *Acta Paediatr Scand (Suppl)* 1990;**370**:5-15
5 Kelnar CJH. *Growth*. London: Medicine International, 1993:217-23
6 Lyall EGH, Crofton PM, Stirling HF, Kelnar CJH. Albuminuric growth failure. A case of Munchausen syndrome by proxy. *Acta Paediatrica* 1992;**81**:373-6
7 Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. *BMJ* 1992;**304**:173-4
8 Albertsson-Wikland K, Rosberg S. Analyses of 24-hour growth hormone profiles in children: relation to growth. *J Clin Endocrinol Metab* 1988;**67**:493-500
9 Hindmarsh PC, Smith P, Brook CGD, Matthews DR. The relationship between height velocity and growth hormone secretion in short pre-pubertal children. *Clin Endocrinol* 1987;**27**:581-97
10 Ahmed S, Shalet S, Beardwell G. The effects of cranial irradiation on growth hormone secretion. *Acta Paediatr Scand* 1986;**75**:255-60
11 Albertson-Wikland K, Lannering B, Marky I, Mellanda L, Wannholt U. A longitudinal study on growth and spontaneous growth hormone secretion in children with irradiated brain tumours. *Acta Paedriatr Scand* 1987; **76**:966
12 Cowell CT, Quigley CA, Moore B, Kirk JA, Bergin M, Jimenez M. Growth and growth hormone therapy of children treated for leukaemia. *Acta Paediatr Scand Suppl* 1988;**343**:152-61
13 Ogilvy-Stuart AL, Ryder WDJ, Gattamaneni HR, Clayton PE, Shalet SM. Growth hormone and tumour recurrence. *BMJ* 1992;**304**:1601-5
14 Kaplan SL, Underwood LE, August GP, Bell JJ, Blethen SC, Blizzard RM. Clinical studies with recombinant DNA-derived methionyl human growth hormone in growth hormone deficient children. *Lancet* 1986;**i**:697-700
15 Stanhope R, Buchanan CR, Fenn GC, Preece MA. Double blind placebo controlled trial of oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988;**63**:501-5
16 Butler GE, Sellar RE, Walker RF, Hendry M, Kelnar CJH, Wu FCW. Oral testosterone undecanoate in the management of delayed puberty in boys: pharmacokinetics and effects on sexual maturation and growth. *J Clin Endocrinol Metab* 1992;**75**:37-44
17 Stirling HF, Kelnar CJH. Puberty. *Curr Paediatr* 1992;**2**:131-6
18 Stirling HF, Wu FCW, Scarth LG, Kelnar CJH. A double-blind placebo controlled study of growth hormone (GH) treatment in prepubertal short children without GH deficiency. *Horm Res* 1991;**35**(suppl 2):31 [Abstract 119]
19 Stirling HF, Wu FCW, Scarth LG, Kelnar CJH. Treatment of short prepubertal boys without significant growth delay: growth hormone (GH) or oxandrolone, singly or in combination? *Horm Res* 1991;**35**(suppl 2): 32 [Abstract 122]
20 Stirling HF, Wu FCW, Scarth LG, Kelnar CJH. Treatment of delayed puberty in boys: growth hormone (GH) or testosterone undecanoate (TU), singly or in combination? *Horm Res* 1991;**35**(suppl 2):42 [Abstract 164]