ETHICAL ISSUES RELATED TO THE USE OF HUMAN GROWTH HORMONE IN IDIOPATHIC SHORT STATURE

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Abstract

The use of growth hormone therapy in children with idiopathic short stature is a subject of great ethical debate. Problems like: benefits, side effects, safety, costs are discussed. Over the past two decades, the indications for the treatment with growth hormone (GH) in children have changed dramatically, widening from the classic GH deficiency to Turner's syndrome, Prader-Willi's syndrome, chronic renal insufficiency, small-for-gestational age and particularly idiopathic short stature that become medicalised, allowing even the short normal child to become the subject for GH therapy. Every new therapeutical method has the tendency to overcome the initial limitations. The idiopathic short stature is a heterogeneous group and a diagnosis of exclusion.. The ethical debate associated with the attempt to enhance the stature of a short but otherwise healthy child is extremely important. The GH treatment involves considerable financial resources which could lead to objections regarding the possible infringement of the principle of equal chances in case of limited access to treatment due to economic considerations. The principle of autonomy and responsibility in children is a very delicate issue, making the medical decision to use growth hormone individual and disputed (the existence of children who want to be small as adults is questionable). More long-term studies and ethical debates are needed in order to assess opportunity, consequences, efficiency and tolerance of GH treatment in children with short stature.

Keywords: *short stature, growth hormone, medical decision, autonomy, responsability*

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Introduction

The use of the growth hormone therapy in children with idiopathic short stature is a subject of great ethical debate. Prior to the advent of biosynthetic GH in 1985, only the children with classic GH deficiency were eligible for treatment. The natural growth hormone derived from the pituitary of cadavers has been used since 1958 until 1985, when several cases of Creutzfeld-Jacob's disease were reported for individuals that ten to fifteen years before had received cadaver-derived GH . Based on the assumption that the infectious vector causing the disease was transferred along with the cadaver-derived GH, this product was removed from the market. The biosynthetic process of GH involves a chemical synthesis of the DNA fragment encoding the first 24 amino acids and complementary DNA copies of messenger RNA prepared from human pituitary cells. The entire DNA sequence is introduced into a bacterium, Escherichia coli, which enables the synthesis of GH.

In October 1985, the Food and Drug Administration (FDA) approved the new drug named Protropin for use in treating children with growth hormone deficiency or chronic renal failure. In December 1996, the recombinant growth hormone was approved for use in treating girls with Turner's syndrome. In July 2003, FDA approved biosynthetic GH for the treatment of children with short stature of unknown etiology (idiopathic short stature- ISS), sometimes known as " short, but otherwise normal" [1].

A virtually unlimited resource of human pituitary- derived GH has led to an increasing number of approved indications [2]. In Turner's syndrome, numerous studies demonstrate that GH can accelerate growth and lead to a greater height than predicted (an average gain of 9 cm over the predicted height without treatment) [3]. Cases of GH-treated children with chronic renal insufficiency on dialysis or transplant revealed significantly greater growth rates in the first and second year of treatment [4]. The treatment with GH for more than 2 years before the onset of puberty in children born small for gestational age (SGA) sustains an accelerated growth rate and the normalization of height in contrast to untreated SGA control subjects [4]. Children with Prader-Willi's syndrome show a higher growth-rate in response to GH therapy similar to other severly GH deficient children [5], [6]. The treatment with GH will allow some of these children to achieve a height closer to lower adult normal range.

GH treatment and idiopathic short stature

Being short is part of the natural diversity of the human race. Such terms such as "short normal stature", "normal variant short stature" and "familial short stature" have been used for a while [7]. Idiopathic short stature, on the other hand, is a relatively recent term and refers to children who are very short compared to their peers, for unknown or hereditary reasons [8].

There is no universal consensus regarding the definition of idiopathic short stature that remains as a heterogeneous group and a diagnosis of exclusion. The definition should be adapted depending on race, geographical area and even historical period. There is also an absence of generally accepted criteria for

diagnosing: inadequate secretion, partial GH deficiency or dysregulation of GH secretion.

By definition, the GH secretion is assumed to be normal in sense of a normal GH peak after a standard provocation test, but subtle disorders of spontaneous GH secretion may be involved in some children labelled as idiopathic short stature [9]. The fact that biochemical tests for GH deficiency are unreliable led, inevitably, to this grey area of "insufficiency" of GH.

In the past decade, there have been many studies reporting the use of GH therapy in idiopathic short stature. There is a general consensus that the GH treatment leads to an increased growth rate in the first years of treatment, but the evidence, however, rarely extends beyond an apparent gain in final height [2], [9], [10], [11], [12], [13].

Many of the controversies surrounding the treatment with growth hormone are related to the absence of well-defined objectives for therapy, the lack of consensus on definition of short stature, costs, medicalisation of short normal children and the capability of informed consent in children.

The ethical issues associated with the attempt to enhance the stature of a short, but otherwise healthy child, have been renewed [14]. Is idiopathic short stature a social prejudice, and more than that, may it lead to a psychological disability? First of all, the term " idiopathic " is unfortunate since it implies a pathology [4]. In any normal population, there will be short normal children who will be at the lower segment of the Gaussian distribution [8]. Treating short, normal children with growth hormone might open a Pandora box [8]. The treatment of one group of children may create illness in another previously healthy group [15], [16]. It is very important to know if the added height with growth hormone is a real gain for the psychological benefit, or just a placebo effect [8].

There are also important economic issues regarding the growth hormone therapy: there are many children who lack acces to the most basic health care and may seem ethically inappropriate (violation of justice and equity principle) to spend colossal monetary resources to provide GH therapy to anyone who is not classically GH deficient or resistant [17]. But is this opinion acceptable for the parents (for whom every centimeter counts) or for those children who reaching adulthood and having judgment is to late to be treated with GH ?

The biosynthetic growth hormone is one of most expensive treatment regimens available. The annual cost for one child weighing 30 kg is approximately $ 15 000 to 20 000. The cost per inch (2.5 cm) of the adult height growth is estimated to be $ 35 000 to 52 000 [4]. Treatment costs of adolescents using higher "pubertal" doses to maximize adult height can exceed $ 50 000 per year. With the idiopathic short stature indication, it has been estimated that more than 400 000 children aged 4 to 15 years are now eligible for GH therapy. Not all children with idiopathic short stature will be treated with the growth hormone but the cost will still be considerable [18]. There is a debate about whether the growth hormone for idiopathic short stature is a medical treatment or an enhancement therapy. The growth hormone therapy for idiopathic short stature represents one of the major challenges for the health

care system.

Autonomy and responsibility in children are two concepts very difficult to comprehend. Young children do not understand the risks and benefits of therapy and cannot give valid informed consent or assent [2], [4], [19]. The average age of 10.3 years was chosen by health care providers for making such medical decision. But many children with idiopathic short stature are under 10 years of age.

Parents and legal guardians are those who make the decision for their children. It is normal to be concerned that your "short" child is disadvantaged and might be discriminated in school. On the other hand, demands for the treatment may also be motivated, less by concerns for the children, than by aspiration of their parents [20]. The parents' attempt to modify their child's appearance may signal tacit disapproval and make them feel unacceptable as they are [7], [21], [22]. Are there children who would prefer to remain short or adults to accept retroactively the non-use of a cure from various reasons ?

According to the literature, short people have emotional and behavioral problems: social isolation, low self-esteem, less marital success, low job satisfaction [16]. Some authors have suggested that short children are conditioned to behave in a socially immature manner and that the stereotypical anxious, introverted short child could well be the result of "experiences associated with the small stature" [14]. Parental overprotection has in fact been shown to be a strong predictor of victimization by peers in school [14]. Even if short children may report higher rates of bullying or victimization some authors consider that they do not experience significant psychosocial problems attributable to their short stature [23] and that there is no statistically significant relationship between height and friendship, popularity or reputation among peers, and therefore social behaviour, friendship and acceptance among peers had a minimal impact on extreme stature [24], [25]. The Wessex Growth Study (WGS), a prospective cohort study, had a unique recruitment technique of unselected population of short, but healthy children, and has shown no evidence of maladaptation or psychological dysfunction, before, during and after puberty [14]. Because psychological problems are not common in short children, it is not surprising that attentively designed studies failed to demonstrate a relationship between adult height of GH treated individuals and quality of life [4], [24], [25]. This lack of evidence for predictable psychological benefit in children with idiopathic short stature who have been treated with GH does not mean that children with short stature should not be treated with GH [4], [24], [25]. It is acceptable that in children with Turner's syndrome or chronic renal insufficiency, the stress of dealing with other diseases could exacerbate an adverse psychological effect caused by their short stature [4]. Health care providers need to carefully assess the parents' perception of short stature but is questionable whether they could ensure families that children with this condition will not experience social, emotional or behavioural issues compared with their taller peers [23].

On the other hand, although the modern society wants to avoid discrimination, the media promotes aestethic models which disadvantage short or even midle-height

persons.Most sports relate the performance with being tall and some professional standards exclude the short stature (police, army). Even in politics individuals would rather give their vote to taller people expressing power and trust, with notable exceptions of course (but not in the left central area of the gaussian distribution).

There are concerns regarding the safety of GH therapy and the incidence of the side effects in children with idiopathic short stature. To date, GH treatment has been relatively safe, with no significant side effects reported [6], [8], [26], [28], [29].

The experience of the past 20 years has shown that GH therapy in children with idiopathic short stature is generally safe, but continued surveillance is necessary because pharmacological doses used to treat non-GH deficient children continue to rise in response to dose-related benefits in growth out-come. The long-term risks of prolonged treatment with higher doses of growth hormone remain unknown, since there is still no evidence about the potential side effects after long periods of time from treatment [1]. Further studies are important to assess the safety of long-term growth hormone therapy in children with idiopathic short stature [27].

Being tall is indisputably viewed as a benefit in our culture, and is associated with multiple advantages, including higher income, academic achievement, self-esteem and social status [17]. The concepts of normality and abnormality are very difficult to define, as they subsume many sociocultural variables [17].

The stigma of the short stature can be addressed in various ways: parents, teachers, nurses can be important by interacting with the short child [30]. Parents can encourage them to participate in sports and other social activities. Role modelling, promoting positive self-image can improve the child's self confidence.

Conclusions

1. Children with idiopathic short stature and their families must be encouraged to avoid pereceiving height as a disability and to achieve performance on their own terms. Parents of children with idiopathic short stature may need to undergo counselling about the limitations of growth hormone therapy.

2.The medical decision to use growth hormone for idiopathic short stature is controversial and individual. Before starting treatment, physicians should explain to the parents the advantages and disadvantages of daily treatment with growth hormone emphasized on: potential side effects, limited expectations in final height, adequate monitoring, cost and the (unknown long-term) risks.

3. GH therapy would be ethically acceptable in the following cases: children with classic growth hormone deficiency, children with chronic renal failure who are awaiting kidney transplantation, girls with Turner's syndrome, children whose extreme short stature keeps them from participating in basic activities of their daily living, and who have a condition for which the efficacy of growth hormone therapy has been demonstrated.

Idiopathic short stature is one of many conditions for which the elective treatment may, or may not be damaging to patients. Therefore, more studies are necessary to determine the

risks and benefits of this type of treatment.

We believe that GH-treatment in idiopathic short stature is disputable: if analysing the benefits, potential risks (theoretically possible but virtually unattested), autonomy (children with no or limited discernment), justice and equity, the decision involving all four classical commandments of bioethics. The final decision should depend on the value scale of each family although the economic factor remains limited.

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