Growth hormone therapy

Human growth hormone therapy (GH) started over half a century ago using growth hormone collected from human cadaver. In 1958 Raben\(^1\) published data showing the effectiveness of this treatment in a patient with hypothalamic-pituitary dysfunction. This treatment quickly became popular and collection systems were set up to obtain enough pituitary hormone to try to meet the demand. However, this was only possible with the advancement of the science and the introduction of genetic engineering to artificially produce this growth hormone, thus ensuring safe and unlimited supply for uninterrupted therapy. Recombinant human growth hormone (rhGH), besides being available, offered very high rates of effectiveness and safety in the indication approved at that time. That led to the search of effectiveness as growth promoter and eventual metabolic benefits in patients with growth retardation, as a manifestation of other conditions. Therefore, with time, indications were approved for patients with Turner’s syndrome, SHOX gene deletions, Noonan syndrome, Prader Willi syndrome, chronic kidney failure and for small for gestational age children with a low birth weight or short stature who had not caught up their height to acceptable levels.\(^2\) A few years ago rhGH was also included in the United States and Europe, in the treatment armamentarium to promote the growth of children with short-height with no apparent cause, with or without a family history.\(^3\)

Prior to deciding the indication for rhGH therapy, all patients should have an appropriate diagnosis, which requires the participation of a pediatrician and a specialist.\(^4\) After treatment initiation, the patient should be closely followed to ensure the drug’s effectiveness and safety. In this sense, the family physician participation is also critical.

Based on the accumulated experience, after much consideration in different fields, GH treatment effectiveness was evaluated for the different indications not only because of the influence on height but also in relation to the patient’s individual costs and associated benefits.\(^5\) Within this context, at present, indicators are being searched so as to be able to show treatment effectiveness in the short term and quickly identify those patients in whom treatment is ineffective. As far as height, the benefit granted by this long and costly treatment can only be seen when patients reach their final height, although different methods, mainly based on anthropometry, allow to infer in the short and mid run, what the long term effects will be.\(^6\) The age at the onset of treatment, the severity of growth hormone deficiency, the rhGH dose used, the objective genetic height and the patient’s adherence to treatment are all factors that have an influence on therapy success.

The biggest beneficiaries are children with a clearly demonstrated growth hormone deficiency who started replacement treatment at an early age, an adequate dose currently considered at about 35 µg/kg/dia. In these patients total gain in final height is around 2 SD.\(^7,8\) In patients with other disorders affecting growth, apart from requiring larger doses, growth hormone treatment benefits are usually less remarkable, though in most cases they are still enough to justify the physical, emotional and economic effort.\(^9\) On the other hand, it’s important to take into account that the limit is not only related to the gain in height but to the benefit that this effect and others provide to enhancing the patients’ quality of life.\(^10\) For certain diagnostic clusters, especially those in whom growth hormone deficiency is not the cause, patients’ individual responses to treatment are an important variable to underscore. Identifying them requires detailed observation and decision to modify the attitude and advice when dealing with patients and their parents.

Incomplete or inadequate responses should be detected early on in order to reformulate the diagnosis, treatment and possible prognosis, adjust the dose or interrupt treatment temporarily or definitely.\(^11,12\)

Treatment of the adult patient,\(^13\) when it exceeds the pediatrician’s responsibility, presents a similar, difficult to solve problem. Diagnostic confirmation of GH deficiency, except when already present from childhood or based on concrete facts, is controversial. Safe dosage based on weight or body surface area is lower than the one used in childhood. Showing effectiveness becomes even more difficult. Several studies have shown short and midterm benefits but those justifying life-long treatment are still missing.

Even though rhGH treatment is a particular problem for each patient, the related social and economic implications involved force all participants to think and decide behaviors based on
Pulse oximetry screening for congenital heart defects in newborn infants

For several years, studies have been regularly published\(^1\)\(^{-7}\) aiming at defining the usefulness of pulse oximetry as a universal screening method for potentially severe congenital heart defects in newborn infants. Occasionally, some heart defects have no clinical manifestations that would allow their identification during the first days of life. Oximetry is mostly used in duct dependent congenital heart disease (complete transposition of the great vessels and right-ventricular obstruction). Likewise, in left-sided obstructive heart defects (hypoplastic left ventricle, atresia or critical aortic stenosis and coarctation of the aorta syndrome),\(^1\) the patency of the ductus maintains an adequate peripheral perfusion, by sending blood from the pulmonary circuit to the aorta distal to the obstruction.

In all these situations, while the ductus remains patent and with a good blood flow, the newborn may not show obvious clinical signs, especially in the first hours of life. However, sometimes the ductus patency is maintained for a longer time and the newborn may be discharged without suspicion of the underlying pathology. This results in an increased risk for the baby since a few days later when the ductus eventually closes, the newborn is readmitted generally in a poor condition thereby having fewer chances of survival.

Pulse oximetry can detect the decrease in peripheral oxygen saturation as a first sign of these heart defects, favoring an early diagnosis before the onset of signs and symptoms.

This has become very important from a practical standpoint given that for many years, in most maternity centers, newborns are discharged early before 48 hours from birth and even in the first day of life. Therefore, having a method that allows the detection of these diseases in the first days of life, ideally before discharge from the maternity center, would mean a major advance in this field.

A recent systematic review and meta-analysis\(^8\) includes a comprehensive search. Thirteen stud-
ies from a total of 552 were selected with a total of 229,421 newborns. The most important of these studies is from the same group and was published in 2011 with over 20,000 newborns from 6 maternity centers in the United Kingdom.9

The most important results of the meta-analysis were the following: 76.5% sensitivity (95% CI 67.7-83.5) and 99.9% specificity (95% CI 99.7-99.9) with a false positive rate of 0.14% (95% CI 0.06-0.33). Additionally, they point out that the latter was significantly lower when the screening was done after the first 24 hours of life: 0.05% (95% CI 0.02-0.12) p= 0.0017, without changing the specificity.

No significant differences were found between the screening done on the foot (post-ductal) versus the screening done on the foot and the right hand (pre and post-ductal) simultaneously.

It is important to point out that in all the included studies, positive tests were verified by echocardiography while in the case of negative tests congenital defects records, mortality data or clinical follow-up visits were reviewed up to one year of age.

At this point, it is advisable to review some basic features that a screening method should have for its result to be of practical use and with an appropriate cost-benefit ratio.
1. It should be a significantly severe condition that will remarkably improve with an early diagnosis and treatment.
2. The method should be easy to implement, available to all candidates to undergo the screening and at an affordable cost.
3. It requires the enforcement of an appropriate follow-up system for cases with a positive screening result.

The first two conditions are inherent to the method itself and we believe these are perfectly met in our country, where the use of pulse oximetry has become the standard practice even in places with scarce resources, precisely because it is so easy to implement.

We should pay attention to the fact that since the specificity of method is very high, it is very good to ascertain that a newborn does not have the condition that is being screened (negative test), but that it is less reliable when it is positive (76% sensitivity). This means that some patients in this group will not have heart defects which force us to pay close attention to the third condition, since we are required to implement what is necessary to confirm or rule out the finding.

In these cases, the heart exam and the echocardiography should be done by qualified staff before patients are discharged from the hospital, because if the suspicion is confirmed, management and treatment measures (prostaglandin infusion to maintain patency of the ductus) should often be immediately implemented to prevent severe deterioration of these newborns from occurring and remarkably improve their prognosis.

We believe that the different realities in our setting make this implementation more complex in some places where consultation with a pediatric cardiologist might be difficult and slow.

In short, and as the meta-analysis authors say, after analyzing the data obtained from these studies there is no doubt regarding the usefulness of screening all newborns for this condition; hence, maternity centers should find the means to put it into practice.

It is also worth considering that it is better for oximetry to be done after the first 24 hours of life since, by reducing the number of false positive results, the cardiology visits will also be fewer.

It was easy to implement this screening in our practice. The screening was done by a nurse along with standard routine controls, always after the first 24 hours of life. Saturation is checked on the right hand and one foot and, following the recommendations provided by most of the studies, the following cutoff points are taken into account: saturation less than 95% or a difference greater than 3% between the pre and post-ductal value.

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