Delayed puberty and hypogonadotropic hypogonadism. Differential diagnosis and treatment
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SUMMARY

This thesis describes a method enabling a prospective differential diagnosis to be made between delayed puberty (DP) and hypogonadotropic hypogonadism (HH). The influence of androgen administration on the gonadal feedback system of patients with delayed puberty was also studied.

Chapter 1 is a review of the physiology of sex hormones and gonadotropins in males. The different factors and mechanisms which influence the secretion of gonadotropins are discussed briefly. Attention is paid to the new insights into the operation of the feedback system obtained by determination of peripheral endogenous LH-RH levels. A high endogenous LH-RH concentration is not always accompanied by high serum LH levels; a relatively high estrogen concentration in the plasma results in an increased endogenous LH-RH secretion together with a low peripheral LH level. LH is present in two functional pools, viz. one where LH is released rapidly by a small stimulus and one which secretes LH by means of protein synthesis after a greater and/or prolonged LH-RH stimulation. The pattern of FSH release is not suggestive of a two pools' system.

Chapter 2 describes the development of the gonadal feedback system. Until the adult phase 4 periods are distinguished, viz. the fetal period, postnatal period, prepuberty and puberty. Recent studies show that prior to puberty, notably in the fetal period and shortly after birth, there is temporarily already a considerable gonadotropic stimulation in comparison with the low gonadotropic stimulation later found during prepuberty. The changes in the gonadal feedback system occurring at the start of and during puberty are described. Because of the elevation of the feedback setpoint a higher LH-RH secretion by the hypothalamus takes place, successively followed by a higher gonadotropin secretion and a higher testosterone secretion. Moreover a pulsating gonadotropin secretion appears (especially of LH), firstly only at night, and at the end of puberty a positive LH feedback develops. Mention is made of the recent indications of a possible role of the augmented androgen secretion by the adrenal gland (adrenarche) that could promote an elevation of the feedback setpoint through accelerated maturation of the hypo-
thalamus. Longitudinal studies reveal that male puberty is delayed when it has not yet started after the 14th year. By agreement a case is considered typical of delayed puberty only after the 15th year. The distinction between delayed puberty and isolated hypogonadotropic hypogonadism is often impossible even with stimulation tests carried out by means of LH-RH, HCG and clomiphene. Literature data on these stimulation tests are discussed.

Chapter 3 discusses patients and methods. The 33 patients examined, in whom no deficiency of other pituitary hormones could be demonstrated, were divided into 4 groups. The hypogonadotropic hypogonadism group (HH) consisted of 7 individuals. The group with delayed puberty (DP) consisted of 10 individuals. The diagnosis was made retrospectively in each case. Of the remaining 16 patients 14 had a delay in skeletal age. In 7 of them (group C) testosterone was between 68-260 ng/100 ml i.e. between prepubertal and adult range. In 9 patients (group D) the plasmatestosterone level was higher than 260 ng/100 ml i.e. in the adult range. Two patients of group D had no delay in skeletal age.

Stimulation with LH-RH was implemented by intravenous bolus injection of 100 μg of LH-RH and by infusion of 200 μg of LH-RH for 4 hours. HCG stimulation (Pregnyl®) took place by an intramuscular injection of 5000 U/day during 4 days. An LH-RH-clomiphene-LH-RH test was set up: after the first LH-RH injection clomiphene citrate (Clomid®) was started in a dose of 200 mg/day during 7 days; in the morning of the 8th day the LH-RH injection test was repeated.

Determination of FSH, LH and testosterone and statistical analysis are described.

Chapter 4 gives results and conclusions obtained with the stimulation tests. LH-RH injection does not result in a different gonadotropin response in DP and HH. High and low responses are found in both groups. The rise of LH and FSH after LH-RH in the DP group is independent of skeletal age.

Infusion of LH-RH gives a difference between the HH and DP groups as regards the maximum LH serum level attained during the infusion, there being also a difference in LH level between both groups after 120, 180 and 240 minutes. This difference between the groups cannot be explained by the differential diurnal variation of the LH level. It could be that the LH levels have different diurnal variations, higher after the 15th year, lower, HH and DP. These diurnal variations in LH level are not seen in the synthetic conditions in the stimulation tests. This rise in LH after clomiphene LH-RH stimulation would be greater in patients of the HH group than in the DP group.

After stimulation of the DP group is greater than that of the HH group previously. If the rise of LH is not higher to the LH-RH stimulation does not result in any rise of testosterone, it was not found by the patients of the HH group. The secondarily induced LH-RH of the HH group is not different than the group HH. The plasma LH level increases after the induction test as regards the secretion of the abdo-

An uncontrolled stimulation test injection of clomiphene citrate.

On comparing the LH-RH stimulation primary response in patients of the HH and DP groups there was a difference in LH response after the LH-RH injection test a difference between DP and HH group.
groups can not be used in the individual case as a prospective differential diagnostic due to the existing overlap. The comparison of the LH level after 240 minutes with the level after 30 minutes or with the mean value of the levels after 15, 30 and 60 minutes does have differential diagnostic value. In the DP group the LH level is higher after 240 minutes in both instances. In the HH group it is lower. HH and DP groups differ in their ability to release LH from the synthesis related pool. This might be explained by different conditions in the fetal and postnatal periods: the then normally occurring increased endogenous LH-RH stimulation of the pituitary would be present in the DP group, but not or to a lesser degree in the HH group.

After stimulation with HCG the testosterone response in the DP group is greater than in the HH group. But this difference, like the previously mentioned maximum LH response during infusion, cannot be used in individual differential diagnosis either. The higher rise of testosterone seen after HCG in the DP group is also explained by the prior difference in gonadotropic stimulation that occurs secondarily to the previously mentioned difference in endogenous LH-RH stimulation. This coincides with the known fact that HH patients who have been submitted to prolonged HCG treatment continue to demonstrate a good reaction to a short HCG stimulation after discontinuation of the treatment and subsequent low testosterone level. The positive shortloop influence of androgens on the induction of LH receptors in the Leydig cell during the postnatal differentiation described recently in rats, is an argument in support of the above.

An unchanged level or fall of testosterone 4 hours after LH-RH injection does not fit in with a diagnosis of delayed puberty.

On comparison of the gonadotropin response to the LH-RH injection prior to and after clomiphene there is a difference between the HH and DP groups. The LH response to LH-RH in the HH group after clomiphene is greater than before. In the DP group the LH response to LH-RH after clomiphene is less than before. Thus this test appears to offer a prospective differential diagnostic between DP and HH. Its speculative explanation is based on the supposition that both in the HH group and in the DP group LH secre-
I is inhibited at the pituitary level by the intrinsic estrogen activity of the antiestrogenous clomiphene, that is prominent in this environment poor in sex hormones, while at the hypothalamic level LH-RH is inhibited in the DP group and not in the HH group: the consequence is a difference in LH amount releasable by exogenous LH-RH.

In chapter 5 the effect of the administration of testosterone as a monthly injection of Sustanon 250 administered to the DP group during 6 months is discussed. Besides the expected direct effect on the development of secondary sex characteristics and growth the follow-up examinations, made 10½ months later on the average, reveal that in all patients some pubertal maturation has taken place in the hypothalamic-pituitary-gonadal axis: the mean basal plasma testosterone level rose from 43 ng/100 ml to 288 ng/100 ml. Although there are some indications that androgens accelerate the maturation of the hypothalamus and consequently its pubertal change this is still uncertain.

This study has shown that it is possible to make a distinction between hypogonadotropic hypogonadism and delayed puberty using a LH-RH infusion and LH-RH clomiphene-LH-RH test. It has also shown that a (short) treatment with androgens in boys with delayed puberty does not impair testicular growth and may possibly induce accelerated pubertal development.