A novel treatment for delayed puberty?

Puberty is a complex physiological process that culminates in the attainment of sexual maturity and the potential for reproduction and fertility. The process is regulated by the hypothalamo-pituitary-gonadal (HPG) axis, which is initially activated prenatally and during infancy, followed by a period of latency until its reactivation in later childhood. The age of pubertal initiation is highly variable (8-12 years in females, 9-14 years in males). The exact stimulus that leads to a reactivation of the HPG axis at the time of puberty is largely unknown; however recent data have suggested a role for factors such as Kisspeptin and Makorin ring finger protein 3 (MKRN3) in the initiation of the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) with consequent gonadotropin pulsatility leading to gonadal sex steroid secretion (1). Puberty may be pathologically early, but is more frequently delayed, particularly in males.

Pubertal delay may be due to a number of causes, and these include a failure to activate and maintain gonadotrophin secretion following the pulsatile secretion of GnRH (hypogonadotrophic hypogonadism) (2). This may be congenital, when it can be caused by mutations in one or more of a number of genes regulating GnRH and gonadotrophin secretion, or acquired due to the presence of tumours, inflammation (eg Langerhans Cell Histiocytosis) or infiltration (eg Thalassaemia) (3). However, the most frequent cause of delayed puberty presenting to paediatric and adolescent endocrinologists is Constitutional delay of growth and puberty (CDGP) (2). This is a variant of normal puberty that appears to be commoner in males, and is characterised by delayed maturation of the HPG axis with a consequent lack of gonadal sex steroid secretion and sexual development. Short stature with reduced growth hormone (GH) secretion and a low concentration of insulin-like growth factor 1 (IGF-1) may be associated with a reduced growth velocity, as GH secretion is highly dependent on sex steroid production during adolescence. The condition is benign and self-limiting, but may be associated with considerable psychological distress and poor self-esteem which may impact on both academic attainment as well sporting prowess. The cause is largely unknown, although 50 to 75% of patients with CDGP have a family history of delayed puberty (2). Recently, a molecular basis has been identified in some cases, with mutations in *IGSF10* being identified in some familial cases (4). The diagnosis is largely one of exclusion, and the main differential is hypogonadotrophic hypogonadism; distinction between the two conditions may be difficult and largely retrospective (2, 5, 6). Both conditions may be treated by the administration of low doses of sex steroids (oral/intramuscular/topical testosterone or oral/topical oestrogen) (2,3,7,8). Although this is a safe and effective therapy that is associated with an increase in IGF-1 concentrations with a concomitant increase in growth velocity, improvement in sexual maturation, and psychological wellbeing, it could nevertheless potentially be associated in males with reduced testicular volumes as well as bone maturation with a reduction in final height, although long-term data are lacking. Other therapeutic modalities include the use of gonadotrophins, which have been used in a small number of cases where the diagnosis of hypogonadotrophic hypogonadism is highly likely or confirmed (3). It should not be used in patients with CDGP, as although this may be associated with gonadal development, the treatment is nevertheless cumbersome and expensive.

In this issue, Raivio et al. report the findings of a multi-centre, randomised, controlled, open-label trial comparing the use of a third generation aromatase inhibitor, peroral Letrozole, with monthly low-dose intramuscular testosterone injections given over a 6 month period, with a further 6 month follow up period (9). Aromatase inhibitors prevent the conversion of androstenedione to estrone and testosterone to estradiol, with the desired outcome of delayed epiphyseal maturation and a potential increase in final height. They have previously been used in patients with idiopathic short stature and delayed puberty (10-12). In this study, Letrozole treatment led to increased concentrations of LH and testosterone, with stable Inhibin B concentrations. On the other hand, low-dose testosterone treatment was associated with suppressed gonadotrophin, testosterone and Inhibin B concentrations. Testicular growth was faster in the boys treated with Letrozole. Although there was no difference in height velocity attained in the two groups, bone age advanced more slowly in the Letrozole-treated boys. BMD increased more in the lumbar spine and hips in the testosterone-treated group, but there was no change in the BMD adjusted for height (BMAD). The authors conclude that Letrozole therapy may represent a novel and

effective treatment modality for CDGP boys with early signs of endogenous puberty.

This is an interesting study, which suggests a novel treatment for a relatively common disorder. The treatment certainly appears to be effective, and its oral mode of administration is an advantage over parenteral testosterone. However, aromatase inhibitors can associated with adverse effects, for example lipid abnormalities and vertebral deformities (13). Although these may not be such an issue with the short-term use of these agents (11), these therapeutic agents should nevertheless be used with caution, particularly in patients with CDGP where the benefits are mainly psychological, and any therapy used should be without adverse effects.

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