Van Wyk and Grumbach Syndrome (A Syndrome of Incomplete Isosexual Precocity and Juvenile Hypothyroidism)

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Introduction

PPrimary hypothyroidism in juvenile population generally leads to retardation of linear growth and delay or even arrested puberty. Rarely, however, sexual precocity may result in a patient with primary hypothyroidism. Such precocious sexual development is however, attended by stunting of growth and retardation of bone age. There is usually pituitary enlargement, which may lead one to misdiagnose the case as pituitary tumour. Serum prolactin, follicular stimulating hormone (FSH), levels are elevated and leutinising hormone (LH), levels are low or normal. The syndrome is completely reversible after treatment with levothyroxine.

Case Report

A nine year old child was brought to the Endocrinology clinic of a large hospital in Jan 98 by her father, with history of having enlargement of both breasts since past several months. The child had been complaining of headache on and off since past 4-5 years which was transient in nature, without any associated vomiting / visual disturbance. The child also had one episode of vaginal bleeding which lasted for 5 days during Nov 97.

The patient was the last of 3 siblings and her brother (aged 12 years) and sister (aged 15 years) were healthy. There was no past history of head injury, encephalitis or seizure disorder. There was no history suggestive of hypothyroidism, but the child had not shown any significant increase in linear height since past 1 year. There was no history of development of other sexual characteristics, like pubic or axillary hair. Examination revealed a height of 113.2 cm (< 3rd centile Tanner & 5th centile ICMR) with proportionate body segments. Height age was 6-7 years and target height was 161.5 + 8.5 cm. Weight 26 Kg (50th centile), weight age 9-10 years. Skin was dry with presence of myoedema. Thyroid size was grade Ib, firm diffuse, with no palpable nodules or audible bruit. Deep tendon reflexes were normal. Breast was B3 size, pubic and axillary hair were absent. External genitalia were prepubertal. There was excess hair growth over the posterior aspect of trunk but Ferriman Galway score was 6 (normal < 8). No virilisation

features were noted. Abdominal examination did not reveal any mass.

X-ray both wrists and hands for bone age assessment showed bone age of 3 years (Fig 1). Serum T3 (RIA) 1.0 ng/ml (0.7-2.1), T4 (RIA) 1.3 ug/dl (4-12) & TSH (IRMA) > 100uiu/ml (0.5-5). Serum LH-1.5 IU/L (5-10), FSH 22.5 IU/L (5-20), oestradiol - 143.8 pg/ml. Serum prolactin - 12 ng/ml (1-20). Ultrasonography of ovaries revealed bilateral polycystic ovaries. Magnetic resonance imaging (MRI) scan of pituitary revealed an enlargement of pituitary measuring 4x1.3 cm with supra sellar extension without significant compression over the optic chiasma (Fig 2). Anti function thyroid peroxidase antibody titre - 1032 IU/ml (normal 40 IU/ml). Patient was diagnosed to have primary hypothyroidism due to chronic thyroiditis and incomplete precocious puberty. Treatment with thyroid hormone replacement (Tab eltroxin) was started, initially with 50 ug/day and gradually built up to reach 200 ug/day. During follow up over past 1 year, she has gained height, thyroid has normalised, no further progression of sexual characters has been noted and vaginal bleeding has not recurred. The repeat MRI scans showed complete regression of pituitary enlargement (Fig-2). The bone age has improved to 9 years (Fig 1). The growth curve shows significant increase in height gain over past 1 year (113.2 to 128 cms).

Discussion

Sexual precocity usually is associated with increase in linear height and acceleration of bone maturity and epiphyseal fusion, ultimately leading to short stature. Long standing untreated primary hypothyroidism is a rare case of incomplete isosexual precocity in both girls and boys and occurs in association with impaired growth and delayed skeletal maturation. Girls have breast development, enlarged labia minora, oestrogenic changes in vaginal smear, usually without appearance of pubic hair [1]. Some girls have irregular vaginal bleeding and solitary or multiple ovarian cysts [2,3]. There is enlargement of pituitary gland demonstrable on computerized tomography (CT) scan or MRI and many a times, this has led to the misdiagnosis of pituitary neoplasm. The serum prolactin levels

Fig. 1 : X-ray both wrists and hands
a) at presentation - bone age = 3 years
b) with treatment - bone age = 9 years

are often elevated. These features are all reversible with thyroid hormone replacement, within a few months [4].

The initial theory, explaining the etiology of this syndrome, was proposed by Van Wyk and Grumbach in 1960 [5]. The low levels of T3 & T4 caused by primary hypothyroidism elicited a rise in TRH secretion, which in turn led to increase in levels of TSH, prolactin and gonadotrophins (LH and FSH). These glycoprotein hormones - TSH, LH, FSH have a com-

Fig. 2 : MRI scan (sagittal cuts) of pituitary gland shows enlarged pituitary with suprasellar extension prior to therapy and normal sized pituitary after treatment

mon alpha subunit. It is thought that a possible hormonal "overlap" results due to negative feedback regulation occurring in primary hypothyroidism - resulting in excess secretion of not only TSH but also LH and FSH. However, the explanation for sexual precocity in primary hypothyroidism remains uncertain, as in uncomplicated juvenile hypothyroidism, puberty development is usually delayed. Moreover, it is now recognised that only FSH level is elevated, LH level is either low or normal [1,6]. The increased FSH release and high FSH/LH ratio is said to be responsible for the increased ovarian oestrogen secretion in girls. (In contrast, in normal puberty, the LH/FSH ratio is high). The increase in FSH level occurs in response to increase in TRH level seen in primary hypothyroidism. Interestingly, in such patients, LHRH injections do not increase FSH level. Thus, incomplete sexual precocity, increased prolactin level, are a sequel of increase in TRH levels, increased sensitivity of breast and gonadotropes TRH or both. This also ex-

plains the rapid reversal of sexia, precocity, normalisation of FSH and prolactin levels, and reduction in pituitary enlargement after treatment with thyroxine, which was so, in this patient. Thus, the entire mechanism of precocity is believed to be FSH mediated, independent of any LHRH. Hence, such precocity is now thought to be incomplete sexual precocity. A similar precocity is known to occur in males also [7,8]. In most boys with juvenile hypothyroidism and precocity, the testes are enlarged because of increase in size of the seminiferous tubules. Signs of virilization and Leydig cell maturation are absent. Plasma testosterone concentration is prepubertal. A direct effect of hypothyroidism on the prepubertal testes leading to overproliferation of Sertoli cells also has been advanced as an explanation of enlarged testes [9].

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