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Primary Hypothyroidism with Precocious Puberty and Pituitary Hyperplasia

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Abstract
Hypothyroidism is generally associated with delayed puberty. However it may sometimes present with incomplete precocious puberty. Also hypothyroidism may lead to pituitary hyperplasia as a feedback tumour. We present a case of 7and ½ year old hypothyroid girl who presented with an episode of vaginal bleed, and pituitary enlargement mimicking macroadenoma which subsided after 2 months of Levothyroxine replacement.

Introduction

Puberty is a transition phase of growth whereby a sexually immature person is transformed into a sexually mature one. Occurrence of puberty early or late has various effects apart from causing psychological concerns and worry. Precocious puberty leads to increased growth velocity with rapid epiphyseal fusion, leading to paradox of tall stature in childhood and short final height. However, hypothyroidism is unique as a cause of precocious puberty as it is characterized by decreased bone age and growth velocity. Hypothyroidism may cause precocious puberty by following mechanisms[1]:

1) Elevated TSH level cross reacts with FSH receptor
2) Low level of thyroid hormone might simultaneously activate release of LH,FSH and TSH
3) Another possibility is that hypothyroidism may cause hypothalamic encephalopathy that impairs the normal tonic suppression of gonadotropin release.

The high PRL levels that sometimes accompany this disorder may result from a deficiency in PIF secretion, increased secretion of TRH, or increased sensitivity to TRH secretion.

Case History

7&$^{1}/_{2}$Year (DOB-17 JULY,2008) old girl presented in endocrine OPD of Medical college Kolkata with breast budding noted over last two months with a single episode of bleeding per vagina 5 days prior to admission without growth of axillary hair and pubic hair.The bleeding was small in amount and noticed by mother as blood spots on undergarments. There was no history of local trauma or discharge, foreign body insertion, bleeding from any other site, or difficulty in micturition. She was the first child born full term normal vaginal delivery with cephalic presentation and a product of non-consanguineous marriage in a low socio economic status family. Patient achieved milestone at normal time and received vaccination at usual time.Her scholastic performance was average. There was no history to suggest prior central nervous system insult, raised intracranial pressure, polyuria, polydipsia, or ingestion of hormonal preparations.There was no history of difficulty in vision.There was no family history of a thyroid disorder or precocious puberty in family.

On examination:

Height-107.8 cm(<3rd percentile) Height SDS : -2.35

Mother Height- 150.1 cm Father Ht-157.2 cm

Target Ht-147.1 cm

Weight- 21 kg BMI- 18Kg/m2

SMR- B2P1 no axillary hair,Vaginal mucosa dull, no signs of virilization ,Goiter gr 1, no café –au-lait spots or bony abnormality , Fundus: normal , no pappiledema

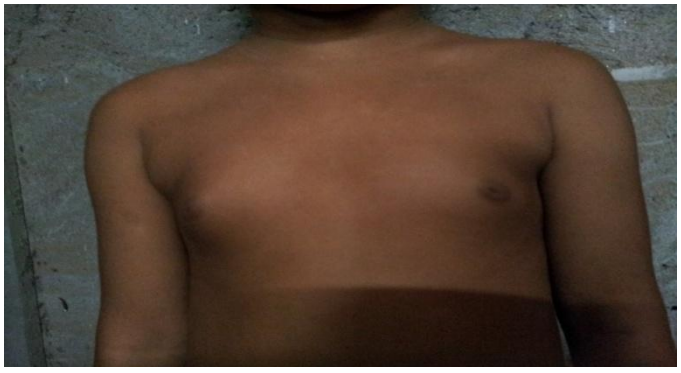

Fig 1: Breast budding ; Tanner B2

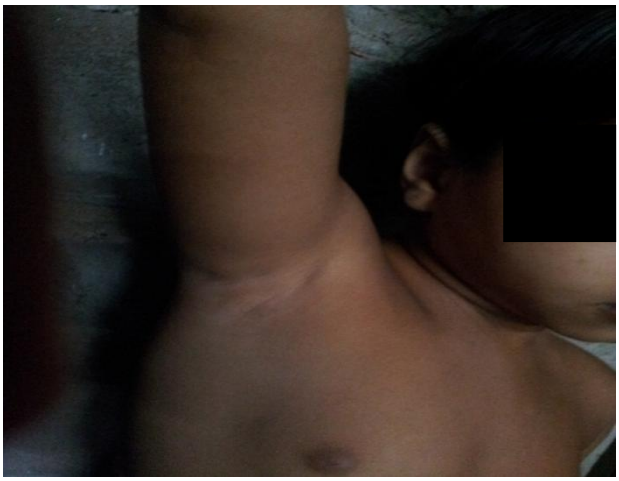

Fig 2: No axillary hair

Investigations

Hb	9.6 g/dl	FT4	0.91 ng/ml
MCV	91fl	TSH	42.62 µIU/ml
MCH	30		
Tlc	6700/cmm	GnRH Stimulation test	Positive
Platelet	2.5 lakh/cmm	LH 0 min	<0.09µU/ml
LH	1.37µU/ml	LH 40 min	8.5µU/ml
FSH	2.39 µU/ml	LH 4 Hr ESTRADIOL 4hr	6.33µU/ml 15pg/ml
Serum cortisol (8AM)	16.8		

USG Pelvis-Uterus 47.2 *16.2mm longitudinal scan

24.0 *14.7 mm transverse scan

ET 5mm

RO-20.1 *17.6 mmmultiple subcentrimetric peripheral follicle noted

LO- 20.7* 18.0mm

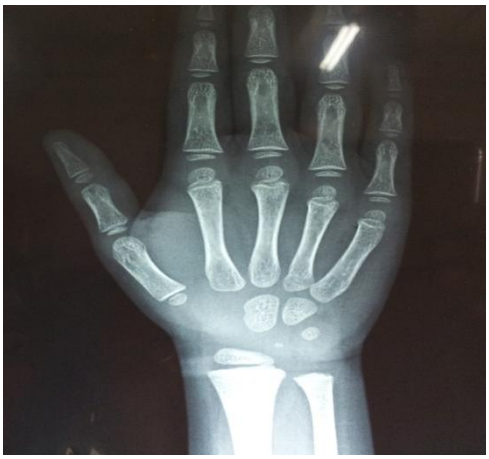

Fig: 3 X ray hand for bone age -3years to 3 &1/2 years

MRI pituitary and hypothalamus was suggestive of pituitary macroadenoma

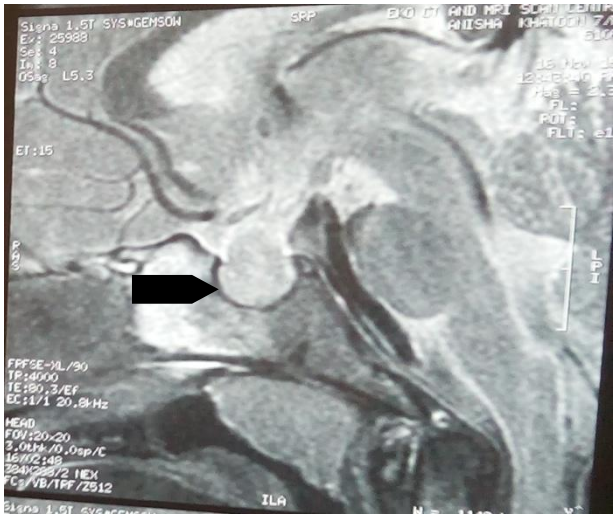

Fig 4: Pituitary hyperplasia mimicking macroadenoma

Treatment

Patient symptoms (vaginal bleed and breast budding), decreased bone age and pituitary enlargement were all considered to be due to hypothyroidism. As the patient was clinically stable and without any visual field defect Patient was treated with levothyroxine 50 microgram OD and was followed after 2 months. In two months her TSH level had come to normal. In the meanwhile there was no recurrence of menstrual bleed. Repeat MRI showed resolution of tumour mass with partial empty sell a without any history of episodic headache, vomiting or loss of consciousness in this period.

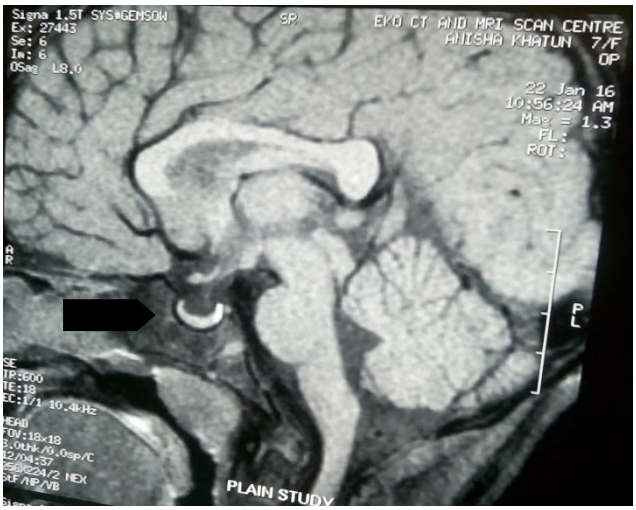

Fig 5: Resolved pituitary mass with partial empty sella

Discussion

Thyroid functions have profound effect on puberty. Very commonly untreated hypothyroidism leads to delayed puberty. Although rarely but sometimes, untrated hypothyroidism may present as precocious puberty[(2)]. Boys in such cases present with macroorchidism while girls may present with the larche with or without galactorrhea, followed by menarche with absence of hair development. Although puberty is precocious, height gain is poor because of loss of contributory action of thyroid hormone on bone. These features were present in our case, so diagnosis of hypothyroidism could be easily made after excluding local causes of bleeding How hypothyroidism leads to precocity , has been explained differently. Wyk and Grumbach suggested that this could be due an overlap in negative feedback regulation with leading to increased secretion of gonadotropins and thyrotropin (both share common α subunit) in response to thyroid deficiency[(1)]. But although gonadotropins are elevated[(3,4)] in these patients, these have been observed to be GnRH unresponsive or bioinactive in earlier studies. However GnRH stimulation test done in our patient was positive, charecterised by LH value in pubertal range . But there was no advancement of skeletal maturation characteristically associated with elevated gonadotropin states. Also suggested is that excess TSH induces FSH like-effects on the gonads. This leads to multicystic ovaries, uterine bleeding, and breast enlargement. However, pubic hair growth does not occur generally as growth of pubic hair requires long duration estrogen, androgens and supportive actions of thyroid hormone. Hence, precocious puberty due to hypothyroidism behaves like an incomplete form of precocious puberty.

Pituitary tumorous hyperplasia may occur in primary hypothyroidism due to negative feedback. Autoimmune thyroiditis is most common cause of primary hypothyroidism. Autoimmune thyroiditis is a gradual disease and patient may not seek

clinical advice early. Also, hypothyroidism may not be diagnosed early if high suspicion is not maintained. Damage of thyroid tissue start early and dysfunction of thyroid hormone synthesis and secretion appears later. As serum FT3 and FT4 concentrations are reduced, this causes weakness of inhibition to hypothalamic TRH secretion and pituitary TSH secretion through a long loop feedback modulation mechanism. Then the hypothalamic TRH secretion increases, followed by hyperplasia and hypertrophy of pituitary TSH-secreting cells. These changes lead to enlargement of anterior pituitary and sometimes adenoma. The increased TRH secretion can also stimulate PRL-secreting cells, promote PRL synthesis and secretion. Therefore hyperprolactinemia and galactorrhea are not an uncommon manifestation of primary hypothyroidism. It is difficult to differentiate Pituitary tumorous hyperplasia due to primary hypothyroidism from primary TSH adenoma, only by radio graphic features. However the treatment is totally different. For primary TSH adenoma, microsurgical treatment is preferred; but for pituitary tumorous hyperplasia due to primary hypothyroidism, thyroxine replacement therapy is treatment of choice. Primary TSH adenoma patients may have symptom of hyperthyroidism and goitre, while biochemically serum FT3, FT4, and TSH levels are found elevated and the serum thyroid antibody are negative. However, in patients suffering from pituitary tumorous hyperplasia due to hypothyroidism serum FT3 and FT4 are decreased, TSH level is high and thyroid antibody is positive.

Substitute therapy is the most important treatment for hypothyroidism with thyroid hormone replacement, the negative feedback loop is re-strengthened and hypothalamic TRH and pituitary TSH secretion decreases, followed by decrease in feedback pituitary adenoma. Ozbey et al. once reported thecase of a patient suffering from a large pituitary adenoma (confirmed by pituitary MRI scan) secondary to primary hypothyroidism, hyperprolactinemia and amenorrhea[(5)]. After treatment with L-T4, plasma T3, T4, TSH, PRL and menstruation returned to their normal ranges, and the large pituitary adenoma disappeared in MRI scan. Hence it was concluded that the large pituitary adenoma was caused by the hyperplasia and hypertrophy of TSH and PRL secreting cells.

So we could think that thyroxine was the more preferred treatment for patients suffering from primary hypothyroidism with premature menarche and pituitary enlargement .Two months after levothyroxine supplementation (50 µgm) patient T3 T4 TSH returned to normal, there was no recurrence of vaginal bleed and the pituitary enlargement, which appeared to be macroadenoma, subsided .There was no history of headache or vomiting to suggest any apoplexy in the pituitary mass

Conclusion

Primary hypothyroidism may sometimes cause precocious puberty. Short stature and delayed bone age may be the clinical clue that hypothyroidism may be underlying cause. Pituitary hyperplasia resulting from hypothyroidism may be so great as to mimick a macroadenoma. If vision is not threatened, levothyroxine supplementation is the treatment of choice. Our experience suggest that levothyroxine supplements corrects both precocious puberty and pituitary hyperplasia.

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