Precocious Puberty: An Unusual Presentation of Hypothyroidism
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Abstract
Hypothyroidism is usually associated with delayed pubertal development but in rare occasions precocious puberty may ensue which is seen in cases of prolonged and untreated hypothyroidism. This is also called the Van Wyk Grumbach syndrome.
Here we present 4 cases of precocious puberty due to hypothyroidism.

Keywords
Hypothyroidism, Puberty, Precocious, Van Wyk Grumbach Syndrome.

Introduction
Hypothyroidism is the most prevalent disorder of thyroid function in children and has many different manifestations (1). The most common manifestation is the slowing of growth velocity which results in short stature (1-3). Other common symptoms are: cold intolerance, altered school performance, lethargy, sluggishness, dry skin, constipation, brittle hair, facial puffiness, mild obesity, delayed teeth eruption. Some rare presentations of hypothyroidism include: pseudotumor cerebri (5-7) abdominal manifestations such as: acute abdominal distension (8), intestinal obstruction and gastrointestinal hypomotility (9), supra clavicular swelling (10), massive pericardial effusion (11), intractable neonatal seizure (12).

Delayed puberty is a common manifestation in hypothyroid patients but rarely can it present as precocious puberty (1). The onset is usually with breast enlargement and vaginal bleeding in girls and testicular enlargement without virilization in boys (1). This presentation is also called as Van Wyk Grumbach syndrome. Recognition of this syndrome is very important because symptoms regress with thyroid hormone replacement and patients can enter into true puberty at its appropriate time (13). Looking for hypothyroidism in girls with ovarian masses and precocious puberty is important in order to avoid surgery on the ovaries.

Here we report 4 cases of precocious puberty due to hypothyroidism. One of them is a girl with Down syndrome.

Case 1
An 8 years old girl presented with abdominal pain, anorexia and vaginal bleeding with one month duration. Her weight was 21 kg (10-25 percentiles on CDC growth charts), her height was 106 cm (below 5th percentile on CDC growth charts). Her breast was tanner stage 4. Pubic hair was not present. We also noticed a grade 2 goiter too. Abdominal sonography showed two cystic masses in both ovaries. She underwent...
surgical operation with the suggestion of ovarian tumor. But pathologic examination revealed follicular cysts. Her hormonal profile was as below:
T4: 3/1 mg/dl, TSH > 100 miu/ml, FSH: 6/3 miu/ml, LH: 1/8 miu/ml, estradiol: 321 pg/ml.

She was diagnosed with hypothyroidism and treatment with levothyroxin was initiated. After 3 months her breast enlargement regressed and vaginal bleeding discontinued and she experienced 3 cm increase in her height.

Case 2
A 9 years old girl presented to the endocrinology clinic with the complaint of short stature and periodic vaginal bleeding since 6 months ago. On initial physical examination her weight was 24 kg (10-25 percentiles on CDC growth charts) and her height was 108 cm (below 5th percentile on CDC growth charts). Her breast was Tanner stage 3. Pubic and auxiliary hair was absent. She had a grade 2 goiter too. Her bone age was retarded and was consistent with 5 years. On abdominal sonography multiple ovarian cysts were reported. Her hormonal investigation was as follows:
T4: 2/1 mg/dl, TSH > 100 miu/ml, FSH: 4 miu/ml, LH: 2/1 miu/ml, estradiol: 260 pg/ml.

Thus the diagnosis of hypothyroidism was made and treatment with levothyroxine was started and after 10 weeks her breast size regressed, ovarian cysts disappeared and she experienced 4 cm increase in her height.

Case 3
A 10 years old girl presented due to short stature and two periods of vaginal bleeding. Her height was 122 cm (below 5th percentile on CDC growth charts) and her weight was 28 kg (10-25 percentiles on CDC growth charts). Her breast was Tanner stage 3. Pubic and auxiliary hair was absent. Thyroid gland was normal size and goiter was not noted. Her bone age was about 8 years. On abdominal sonography uterus and ovaries were normal.

Her hormonal profile was:
T4: 5 mg/dl, TSH>100 miu/ml, FSH: 4 miu/ml, LH: 1/1 miu/ml, estradiol: 181 pg/ml.

Treatment for hypothyroidism was started and after 2 years follow up she had 20 cm growth catch up.

Case 4
A 7 years old, Down syndrome girl presented due to 2 times menstruation. Her height was 106 cm (below 5th percentile on CDC growth charts), her weight was 25 kg. She had a grade 2 goiter. Her breast was Tanner stage 3 and her pubic hair Tanner stage 2. Her bone age was 5.5 years. She had no ovarian cysts on abdominal sonogram.

Below is the report of her hormonal investigations:
T4: 5 mg/dl, TSH > 100 miu/ml, FSH: 7/6 miu/ml, LH: 2/8 miu/ml, estradiol: 195 pg/ml.

Treatment with levothyroxine was started and after 6 months of therapy, signs and symptoms of puberty regressed.

Discussion
Hypothyroidism is the most common disturbance of thyroid function in children (4). Delayed puberty is a common manifestation of untreated hypothyroidism but precocious puberty can occur in as many as 50% of children with severe longstanding and untreated hypothyroidism (4). Hypothyroidism associated precocious puberty is also called Van Wyk Grumbach syndrome. It was first described in 1960 by Van Wyk and Grumbach (17). In girls the onset of symptoms is with thelarche followed by menarche and characteristically there is no development of pubic or axillary
hair and opposite the patients with true precocious puberty these patients have a decreased linear growth (4). In patients with isosexual pseudo precocious puberty, the presence of an ovarian mass would suggest ovarian tumors but in such cases, the bone age is advanced. Hence, the presence of a retarded bone age in patients with precocious puberty is an important clue for the diagnosis of van wyk Grumbach syndrome (14).

In all our four cases the typical clinical clues of hypothyroidism which are short stature and delayed bone age were present, so the diagnosis of hypothyroidism could be easily made. Other important manifestations of longstanding hypothyroidism such as bilateral ovarian enlargement with multiple cysts, increased levels of gonadotropins mainly FSH and estradiol were also detected in our cases. This syndrome can be diagnosed by the recognition of its clinical features and appropriate confirmatory laboratory tests (13).

Our fourth case was a girl with Down syndrome. This syndrome predisposes the patients to thyroid hormone disorders and it’s recommended that these patients undergo periodic evaluation of their thyroid function (16).

The exact hormonal mechanism of hypothyroidism associated precocious puberty is not understood. Wyk and Grumbach explained that in response to thyroid hormone deficiency overproduction of gonadotropins as well as thyrotropin (which both share common α subunit) occurs (17). But these elevated gonadotropins have been shown to be bioinactive in earlier studies and also absence of characteristics of gonadotropin excess such as advanced bone age in these cases makes the gonadotropin excess as the underlying mechanism unlikely (18).

Prolactin theory has also been postulated which says hyperprolactinemia as a result of chronic stimulation of TRH increases the sensitivity of ovaries to even very small amounts of gonadotropins before puberty (20).

Another theory is that interaction of TSH with human FSH receptor is the possible mechanism of this syndrome (19). Elevated levels of TSH produce FSH–like effects on the gonads in the absence of LH effects (4). This seems to be the most likely mechanism of this syndrome.

All symptoms of this syndrome resolve with thyroxine replacement therapy, the endocrine abnormalities subside, the ovarian cysts decrease in size or disappear (20), as seen in our patients during their follow up.

Conclusion
Children with signs of precocious puberty and short stature and delayed bone age should be sought for hypothyroidism. Patients with Down syndrome are at increased risk for thyroid problems and should be tested for thyroid function if decreased growth or signs of precocious puberty ensue.

Acknowledgments
The authors wish to express their thanks to their patients and their families for their cooperation.

References