CASE REPORT

Multiple Pituitary Hormone Deficiency, Empty Sella and Ectopic Neurohypophysis in Turner Syndrome

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Background: Multiple pituitary hormone deficiency and Turner syndrome have overlapping features in peripubertal girls and is a diagnostic challenge. **Case characteristics:** 16-year-old girl having Turner phenotype undergoing evaluation for severe short stature and pubertal arrest. **Observation**: 45,X karyotype, and multiple pituitary hormone deficiency with empty sella. **Intervention:** Levothyroxine, growth hormone and ethinyl-estradiol replacement resulted in 11 cm height gain with attainment of puberty over 2 years **Message:** Patients of Turner syndrome with height <3rd percentile (Turner specific charts) warrant additional pathology evaluation.

Keywords: *Gonadotropin deficiency, Growth hormone deficiency, Hypothyroidism*.

Short stature is a consistent feature in Turner syndrome [1], and is seen in nearly 100% patients. Ectopic neurohypophysis and/or empty sella has been observed in 43% children with growth hormone (GH) deficiency, and is even more common in multiple pituitary hormone deficiency (MPHD) [2]. MPHD and Turner syndrome have overlapping features in girls during peripubertal age with both presenting with short stature and pubertal arrest. We present a child with MPHD in Turner syndrome.

Case Report

A 16-year-old girl presented with short stature noticed since 10 years of age along with lack of puberty. She had normal childhood, without any history of failure to thrive, head injury or polyuria. Maternal age of menarche was 14 years. Examination revealed significant short stature (Height 127.2cm; standard deviation. -6.06), multiple facial nevi (***Fig.* 1a**), cubitus valgus and goiter. Sexual maturity rating was pre-pubertal. Bone age (Greulich Pyle) was 10 years. Ultrasonography revealed infantile uterus with lack of visualization of ovaries. Karyotype was 45,X. Height plotted on Turner syndrome specific growth chart (TSGC) was <5thpercentile [1]. Hormonal evaluation revealed secondary hypothyroidism and hypogonadism (low basal and post GnRH analogue stimulated LH). Serum electrolytes were normal. Anti thyroid peroxidase antibody titer was elevated (224 U/mL; normal <35 U/mL). Serum IgA anti-tissue transglutaminase antibody levels were normal (0.2 AU/mL; normal <8 AU/mL).

Levothyroxine was started at 50 µg/day. Evaluation of GH status 4 weeks later revealed GH deficiency **(*Web Table I*)**. Magnetic resonance imaging (MRI) of brain revealed empty sella with ectopic neurohypophysis near tuber cinerium (***Fig.* 1b**). GH was started at 3 U/night subcutaneously, increased to 4.5U/night after three months. Ethinyl-estradiol 2.5 µg/day was also started, along with calcium and vitamin-D. Reassessment was done 6 monthly. Ethinyl-estradiol was increased by 2.5 µg every 6 months. She gained 5 cm height in first 6 months, 3 cm in next 6 months, and 3 cm in next 1 year when GH was stopped. Two years after diagnosis, her height was 138.2 cm (***Fig.* 1c**), had B3 breast development, and was on 10 µg of ethinyl-estradiol. Following breakthrough bleeding, patient has been receiving monthly medroxypro-gesterone along with ethinyl-estradiol for the last three months, ensuring regular menses.

Discussion

Growth failure in Turner syndrome is characterized by low IGF-1, increased IGF binding protein-3 proteolytic activity, without GH deficiency [3]. This report highlights the occurrence of GH deficiency and MPHD in Turner syndrome. Valenta, *et al*. [4] reported two patients of Turner syndrome with hypogonadotrophic hypogonadism. There are two other reports of this association [5,6]. Association of MPHD and Turner Syndrome, as in our patients, is even rarer [7].

Height of all girls with Turner syndrome should be plotted on TSGC. Those having height <3rd percentile

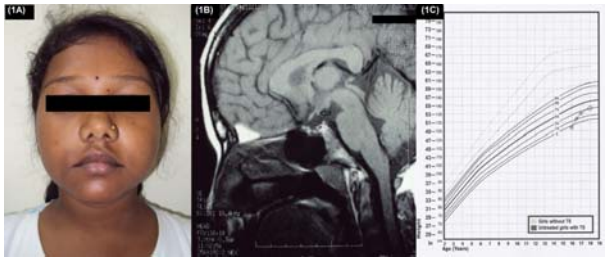

FIG. 1 *(a) Facial profile of patient showing multiple facial nevi, depressed nasal bridge with small mandible; (b): MRI brain sagittal section showing empty sella (white arrow) with ectopic neurohypophysis at tuber cinerium (black arrow); (c): Height curve of our patient following levothyroxine, growth hormone and sex steroid replacement plotted on Turner syndrome specific growth chart.*

should be evaluated for additional pathology. Other warning features include severe short stature, marked bone age delay, and lack of elevated FSH, as seen in our patient. Turner syndrome is classically associated with elevated FSH and LH, a result of hypergonadotophic hypogonadism secondary to primary ovarian failure. A child, whose clinical phenotype and karyotype suggestive of Turner syndrome with normal/low FSH should be evaluated for an associated primary defect in the pituitary/hypothalamus. Elevated anti-thyroid peroxidase antibody titer in our patient is reflective of underlying thyroid autoimmunity. Turner syndrome is well known to be associated with increased occurrence of various autoimmune disorders, which include autoimmune thyroid disorders and inflammatory bowel disease [1].

Effect of GH in Turner syndrome is inferior to that in cases of isolated GH deficiency [8]. Factors associated with improved final height in Turner syndrome include higher baseline height, higher mid parental height, higher GH dose used, younger age at GH initiation and longer therapy [1]. Levothyroxine and sex steroids may have contributed to the better height outcome seen in our patient. Indications for termination of GH in Turner syndrome include bone age 14 years or growth velocity <2 cm/year [9,10]. Recently it has been suggested that early initiation of GH in Turner syndrome before onset of growth failure (before 4 years age), results in 80% children achieving normal stature [3]. Also it has been suggested that early initiation of very low dose estradiol (at 5 years of age instead of at 12 years), along with GH results in additional increase in adult stature by 2.1 cm [10].

Limitations of this report include lack of genetic testing for transcription factor defects causing MPHD. However, most transcription factor defects present in early childhood, except for PROP1 mutation [2]. Clinical profile of our patient did not match with that of any known transcription factor defect. We conclude that any Turner syndrome patient, with height <3rd percentile on TSGC, should be further evaluated for additional conditions.

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