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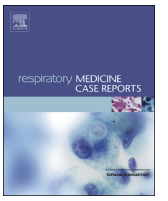

Case Report

Case report of a Hispanic female with cystic fibrosis and short stature

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ABSTRACT

A 10-year-old female with cystic fibrosis (CF), diagnosed by newborn screen, and pancreatic insufficiency was referred by gastroenterology to endocrinology for short stature (Z-score -3.5 SD). She had poor growth velocity and delayed bone age, although stunting of her growth was evident by age 6 years. Her karyotype was consistent with Turner syndrome (45,X). Growth hormone therapy has improved her growth velocity; she is tolerating it without side effects. At 12 years old, she has delayed puberty due to primary ovarian failure and will initiate estrogen replacement.

Her case highlights the importance of a comprehensive evaluation for short stature in individuals with CF. Poor growth velocity and extreme short stature should not be dismissed as expected comorbidities of CF. The differential for causes of short stature is broad, with some etiologies having significant sequalae and increased morbidity beyond that already seen in CF.

1. Introduction

Short stature in patients with cystic fibrosis (CF) is multi-factorial including CFTR gene mutation, comorbid pancreatic insufficiency resulting in malabsorption, abnormalities in the GH-IGF1 axis due to inflammation, and use of glucocorticoids [1]. Children with CF with poor growth including height, weight and height-for-weight or body mass index, have increased mortality and morbidity including increased pulmonary complications [2,3]. Early growth trajectory affects later survival even before manifestations of CF become obvious [4–6]. While short stature is recognized as a clinical feature of CF, subnormal growth velocity or short stature that seems excessive should still be evaluated for other causes of short stature, including celiac disease, chronic liver or kidney disease, thyroid dysfunction, GH deficiency and hypogonadism. Turner syndrome should also be considered in females with short stature.

2. Case report

A 10 years 10 months old Hispanic female with CF (DF508/IVS3-1G > A) and pancreatic insufficiency was referred by her gastroenterologist to endocrinology for evaluation of short stature. The diagnosis of CF was made in the neonatal period after an abnormal newborn screen. Her gastroenterologist followed her for failure to thrive and had optimized nutrition with appetite stimulants (cyproheptadine), nutritional supplements (PediaSure) and pancreatic enzymes. Her height Z-score was -3.5 SDS, giving her the height age of a 6.5 year old. Her growth velocity was 2.7 cm/year which is subnormal for a prepubertal child (Fig. 1). Her bone age

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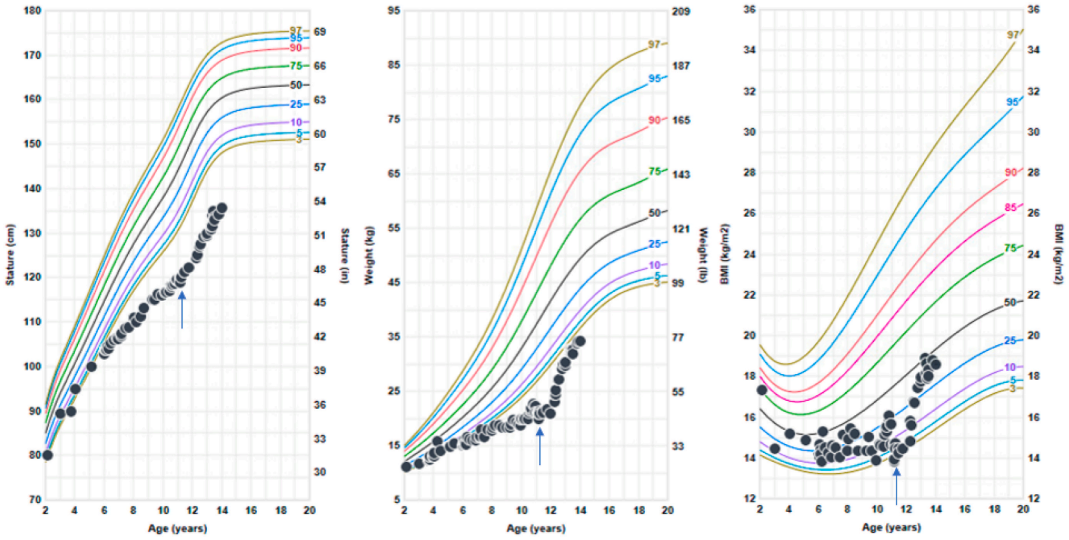

Fig. 1. Growth charts. The patient's height, weight and body mass index (BMI) are plotted on the CDC girls' growth charts. The arrow indicates when growth hormone was initiated.

was delayed at 7 years 10 months. Her mother's final adult height is 5′1″, but multiple maternal family members are shorter than 5 feet. Her father and his family members are reportedly of normal stature.

Additionally, she had normal thyroid function and no history of systemic or inhaled glucocorticoid use. Overall, her pulmonary complications of CF were well controlled; her most recent FEV1 was 91% predicted. Prior to her evaluation, she had had no history of dysglycemia, but her HbA1C and oral glucose tolerance test (OGTT) at time of her endocrine evaluation were consistent with impaired glucose tolerance. Her birth history was notable for being full-term, with birth weight 2.605 kg (7th percentile) and birth length 48.5 cm (36th percentile). She was very short for her age, thin and had digital clubbing, but did not have the classic Turner syndrome phenotype. Due to her poor growth velocity and extreme short stature, a karyotype was performed which revealed 45,X. She was started on growth hormone (GH) therapy with improvement of her growth velocity.

Once diagnosed with Turner syndrome, she was screened for complications and comorbidities associated with Turner syndrome [7]. She had a history of recurrent otitis media with tympanostomy at age 1. Due to her CF, she had been screened for diabetes, liver disease and osteopenia. She had transaminitis and a history of cholestasis. Her dual energy x-ray absorptiometry scan revealed low bone mineral density when adjusted for age, but normal bone mineral density when adjusted for both height and age. Her renal ultrasound revealed a horseshoe kidney. Her audiology testing identified high-frequency hearing loss. She had negative screening for celiac disease, Hashimoto's thyroiditis, and a normal echocardiogram. At 10 years old, she was prepubertal, which is within normal variation. Her labs were not consistent with hypergonadotropic hypogonadism; however, her anti-müllerian hormone level was undetectable, suggesting that gonadal failure was expected.

After 2 years of GH therapy, linear growth improved to the height age of an 8.5 year old and an annualized growth velocity of 5.5 cm/year. Her hearing loss which may have been related to aminoglycoside antibiotic use for treatment of pulmonary infections is improving without intervention. Her transaminitis has similarly improved without intervention. She has not achieved thelarche consistent with delayed puberty. Her labs are now consistent with hypergonadotropic hypogonadism. She will initiate pubertal induction with transdermal estradiol at her next endocrine clinic visit. Her dysglycemia has improved; her recent OGTT and HgA1C have been normal even with GH therapy.

3. Discussion

To our knowledge, this is the first pediatric report and third report of a female with CF and Turner Syndrome. The first two reports [8] were of two women in Germany with CF, diabetes and growth retardation. Unlike prior reports, our patient did not have CF-related diabetes and is Hispanic. CF affects one per 3500 newborns [9]; but only one per 9200 livebirths of Hispanic people [10]. In the 2020 CF Foundation Patient Registry of patients in CF centers in the United States, 9.6% of patients identified as Hispanic [11]. Turner syndrome affects one in 2500–5000 live births, with many fetuses that are affected by monosomy X suffering spontaneous miscarriage resulting in a wide incidence estimate. While CF is an autosomal recessively inherited disorder; Turner Syndrome occurs due to a sporadic event.

Growth is affected in patients with Turner Syndrome and CF. Patients with Turner Syndrome have genetic short stature due to SHOX haploinsufficiency. The average adult height for females with Turner Syndrome is approximately 56 inches [12]. Short stature is a well-recognized complication of CF, and children with CF often have multiple risk factors for short stature. As therapies for CF have improved, so too has the height of people with CF. In the 2020 CF Foundation Patient Registry, less than 10% of people with CF had a height $<5^{th}$ CDC percentile, and the median height of children was at the 38th percentile [11]. However, a child should be evaluated for short stature if their height is more than 2 standard deviations below the mean for age or less than the 5th percentile, or if the

child's growth velocity is subnormal (prepubertal children are expected to grow at least 4–5 cm/year) [1]. Initial management should involve optimizing their health and modifying risk factors for short stature associated with CF including pancreatic insufficiency, undernutrition, minimizing use of glucocorticoids (both systemic and inhaled), and aggressively controlling infections and chronic inflammation [1].

While GH is not uniformly recommended for patients with CF, recombinant GH is recommended and FDA-approved for girls with Turner Syndrome. Girls with Turner syndrome who receive GH treatment can gain approximately 2.5 cm/year, which enables a more normal adult height; however, many do not reach the first percentile for average girls according to the Centers for Disease Control (CDC) growth reference charts [7]. In addition, girls with Turner syndrome have primary ovarian failure with many failing to spontaneously enter puberty. Some have thelarche but fail to progress to menarche and their pubertal development stalls. Height may be further compromised by comorbidities associated with and complications of Turner syndrome including celiac disease, hypothyroidism secondary to Hashimoto's thyroiditis, and chronic disease related to cardiac malformations and diabetes.

For individuals with CF, GH may have benefits in addition to promoting linear growth velocity. In a recent meta-analysis of GH therapy for children and young adults with CF, there was no difference in acute pulmonary exacerbations: need for hospitalization or need for antibiotics [13]. Pooled data in the meta-analysis indicated that GH therapy may have benefits for FEV1 after 12 months of therapy, weight gain, lean body mass, and self-reported body image score [13]. Some trials found an elevation in mean fasting blood glucose in subjects treated with GH compared to subjects not treated with GH which was not clinically significant, and no subjects developed diabetes during the studies [14,15].

It should be noted that GH treatment is known to cause hyperglycemia with increased risk for developing type 2 diabetes [16], and patients with Turner syndrome are at risk for type 2 diabetes. This risk is further increased in this patient's case due to her history of impaired glucose tolerance and CF. This patient will be closely monitored with annual screening for diabetes and symptom screening at all clinic visits. With close monitoring for the potential side effects of GH treatment and her growth velocity, GH can be safely used for this patient.

In summary, our patient's case emphasizes the importance of a broad differential even in patients with rare diseases. Females with short stature should be evaluated for Turner syndrome with a karyotype, as short stature may be the only presenting sign of Turner syndrome.

Declaration of competing interest

None.

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