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Concurrent Van der Woude syndrome and Turner syndrome: A case report

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Abstract

Most cases of Van der Woude syndrome are caused by a mutation to interferon regulatory factor 6 on chromosome 1. Turner syndrome is caused by complete or partial absence of the second sex chromosome in girls. We describe a unique case of the two syndromes occurring concurrently though apparently independently in a girl with Van der Woude syndrome diagnosed at birth and Turner syndrome at 14 years 9 months. Short stature was initially misattributed to Van der Woude syndrome and pituitary insufficiency associated with clefts before correctly diagnosing Turner syndrome. We discuss the prevalence of delayed diagnosis of Turner syndrome, the rarity of reports of concurrent autosomal chromosome mutation and sex chromosome deletion, as well as the need to consider the diagnosis of Turner syndrome in all girls with short stature regardless of prior medical history.

Keywords

Turner syndrome, Van der Woude syndrome

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Introduction

Van der Woude syndrome (VWS) is characterized by pits or sinuses of the lower lip and cleft palate (CL/P, CP) and is the most common cleft syndrome with an incidence of 1:35,000–1:100,000 in Caucasians.[1] It was originally described by Van der Woude[2] in 1954 noting a dominant inheritance pattern with variable penetrance and expression. Murray et al.[3] mapped the gene responsible to chromosome 1q and subsequently Kondo et al.[4] demonstrated that mutation in the interferon regulatory factor 6 (IRF6) gene on chromosome 1q32-41 caused the disease. A summary of mutations within the IRF6 gene associated with VWS is reviewed by Stuppia et al.[5] Further studies have demonstrated mutations in grainyhead-like 3 (GRHL3), which also led to VWS according to Peyrard-Janvid et al.[6]

Turner syndrome (TS) affects approximately one in 2500 live-born females[7] and was originally described by Turner in 1938 as sexual infantilism, webbing of the neck and cubitus valgus. Indeed, the variable phenotype has been further refined to include an array of endocrine, cardiovascular, developmental, psychosocial, genetic, and reproductive issues. Complete or partial absence of the second sex chromosome, with or without cell line mosaicism, is requisite for diagnosis.

Case study

A Caucasian girl with prior diagnosis of VWS presented to our pediatric endocrinology clinic for evaluation of short stature and delayed puberty and was subsequently found to have TS. She was born at 37 weeks gestation to non-consanguinous parents with birth weight 3300 g (40th percentile). Family history included VWS in paternal family members including father, grandfather, uncle, and cousin. VWS was suspected at birth and confirmed by genetic study at age 1 year by parent report (results not available). As a toddler, she had surgical excision of lip pits, repair of lower cleft lip, bilateral soft palatoplasty, adenoidectomy, and several sets of tympanostomy tubes. Her pubertal development was delayed and at presentation to our clinic at age 14 years 9 months had appearance of Tanner 2 breast development, though breasts were mainly of

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adipose tissue, and she had no pubic hair (Tanner 1). She had no menarche. Her height was 141.9 cm (<1st percentile, standard deviation (SD): −3.04; 90th percentile on TS growth curve), weight 45.8 kg (20th percentile), and body mass index (BMI) 22.75 kg/m^2 (80th percentile). Mid-parental target height was at the 50th percentile. Paternal great aunts reported to have adult height less than 5th percentile. She had fullness of the lower lip, surgical scarring of her oral mucosa, and a stocky build, but otherwise her physical exam was unremarkable for specific TS features, for example, no webbed neck, high-arched palate, or cubitus valgus.

Laboratory analysis revealed normal thyroid-stimulating hormone (TSH) and free T4, tissue transglutaminase (TTG), immunoglobulin A (IgA), complete metabolic panel, and complete blood count. Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) specimens were incorrectly handled, and results were not available. Follicle-stimulating hormone (FSH) was clearly elevated (157 mIU/mL (Tanner 2 normal: 1.0–10.8 mIU/mL; Esoterix Lab) and estradiol 2 pg/mL (Tanner 2 normal: 10–24 pg/mL; Esoterix Lab) reflective of hypergonadotropic hypogonadism. High-resolution chromosomal analysis demonstrated mosaic TS (45,X[16]/46,X,i(X)(q10)[3]/47,X,i(X)(q10),+i(X)(q10)[1]). Pelvic ultrasound demonstrated prepubertal uterine size, and ovaries were unable to be visualized. Bone age was delayed (bone age: 13 years 0 months; chronological age: 14 years 9 months). She started on recombinant human growth hormone (GH), as well as estrogen replacement therapy. In light of the new diagnosis, the patient was referred to for echocardiography, electrocardiography, and renal ultrasonography which were normal. Ethical approval to report this case was obtained from Oregon Health & Science University Institutional Review Board and verbal approval provided by the patient.

Discussion

Short stature is the most common, readily recognizable clinical feature of TS.[8] While girls with TS tend to have normal GH secretion pattern, GH therapy is effective in increasing final adult height.[8] Up to 30% of girls with TS will undergo some spontaneous pubertal development;[9] however, ultimately over 90% will have gonadal failure. The decision to begin puberty induction with estrogen therapy must be individualized to the patient and many will require replacement therapy until the time of normal menopause.

A delayed diagnosis of TS is not uncommon. In a single center's experience with the delayed diagnosis of TS in 81 patients, short stature was the most common reason (75%) for ordering a karyotype leading to the diagnosis of TS in childhood (1–11 years).[10] When diagnosed in adolescence (12–18 years), short stature was nearly ubiquitous (93%) but delayed puberty was also present in 57%. Retrospectively, the diagnosis of TS occurred 5 years after height fell below the 5th percentile. Compared to girls with 45, X karyotype who are more often diagnosed prenatally or shortly after birth due to apparent edema, dysmorphic features, or cardiac abnormalities, those with mosaicism more often have delayed diagnosis.[11]

We found no prior report of concomitant TS and VWS in the literature. Indeed, the concurrence of both autosomal mutations and sex chromosome deletion appear to be rarely reported. Only two such occurrences involving TS are previously reported: TS with Costello syndrome (mutation of *HRAS gene* on chromosome 11) at 13 years of age[12] and TS with thalassemia major (mutation of *HBB gene* on chromosome 11).[13]

There is no known common pathway that would suggest a link between VWS and TS in the patient we present; it is assumed these two occurred independently. Using the incidences referenced above, the risk of developing both in a female is 1:87,500,000–1:250,000,000.

Grimberg et al.[14] describe sex differences in patients referred for evaluation of poor growth in a single center and identify girls as being more likely to have organic disease (risk ratio: 2.7) as an underlying cause. Girls were also referred at more severe height standard deviation score (SDS; −2.4 for girls vs −1.9 for boys). Ultimately, 41% of girls (39/96) compared to 15% of boys (27/182) referred had an organic cause. Of the girls with an organic cause, 23% (9/39) had TS.

Conclusion

While concurrent autosomal mutations and sex chromosome deletions are rare, our case highlights the need to consider the diagnosis of TS in all girls with short stature regardless of prior medical history.

Declaration of conflicting interests

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