Williams Syndrome and 15q Duplication: Coincidence versus Association

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Key Words

Central precocious puberty · Duplication 15q · Gonadotropin-releasing hormone · Williams syndrome

Abstract

Williams syndrome is a multisystem disorder caused by contiguous gene deletion in 7q11.23, commonly associated with distinctive facial features, supraaortic stenosis, short stature, idiopathic hypercalcemia, developmental delay, joint laxity, and a friendly personality. The clinical features of 15q11q13 duplication syndrome include autism, mental retardation, ataxia, seizures, developmental delay, and behavioral problems. We report a rare case of a girl with genetically confirmed Williams syndrome and coexisting 15q duplication syndrome. The patient underwent treatment for central precocious puberty and later presented with primary amenorrhea. The karyotype revealed 47,XX,+mar. FISH analysis for the marker chromosome showed partial trisomy/tetrasomy for proximal chromosome 15q (15p13q13). FISH using an *ELN*-specific probe demonstrated a deletion in the Williams syndrome critical region in 7q11.23. To our knowledge, a coexistence of Williams syndrome and 15q duplication syndrome has not been reported in the literature. Our patient had early pubertal development, which has been described in some patients with

Williams syndrome. However, years later after discontinuing gonadotropin-releasing hormone analogue treatment, she developed primary amenorrhea.

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Williams syndrome, also known as Williams-Beuren syndrome (OMIM 194050), is a genetic disorder caused by a hemizygous microdeletion involving elastin and additional genes in the chromosomal region 7q11.23 [Meng et al., 1998; Pober, 2010]. Prevalence of Williams syndrome is estimated to be 1 in 7,500–10,000 [Strømme et al., 2002]. Affected individuals have multisystem involvement including cardiovascular, neurological, endocrine, and behavioral abnormalities. Diagnosis is confirmed by FISH [O’Rand et al., 1985] involving the elastin gene (*ELN*)-specific probes which reveal the presence of a single *ELN* allele rather than 2 alleles [Pober, 2010].

The classic syndrome is described as having typical facies, supraaortic stenosis, infantile hypercalcemia, and variable degrees of intellectual disability with a friendly and outgoing personality. The facial features evolve with age. Young children are often described to have a flat nasal bridge, short upturned nose, periorbital puffiness, long philtrum, and a delicate chin, whereas older patients have slightly coarse features, with full lips, a

wide smile, and a full nasal tip [Burn, 1986]. Endocrine abnormalities reported in Williams syndrome include hypercalcemia (unknown mechanism), impaired glucose tolerance, subclinical hypothyroidism, osteopenia and osteoporosis, and early onset of puberty [Cherniske et al., 2004]. Patients manifest decreased growth velocity in childhood and an early, however attenuated adolescent growth spurt that eventually leads to diminished final adult height [Pankau et al., 1992; Partsch et al., 1999]. Central precocious puberty (CPP) occurs in 1 of 5–6 girls (18.3%) with Williams syndrome and is believed to be gonadotropin dependent [Partsch et al., 2002].

Proximal 15q duplication, involving the critical region for Prader-Willi syndrome and Angelman syndrome, also referred to as chromosome 15q11q13 duplication syndrome (OMIM 608636), has been reported in patients with autistic disorder and varying degrees of mental retardation [Clayton-Smith et al., 1993; Baker et al., 1994; Bunday et al., 1994; Flejter et al., 1996]. The maternally derived aberrations lead to an abnormal phenotype, while the paternally derived duplications in these regions are phenotypically neutral [Cook et al., 1997]. The incidence of 15q duplication syndrome at birth is estimated to be 1 in 30,000 with a sex ratio of almost 1:1 [Schinzel and Niedrist, 2001]. Several types of genotypic aberrations affecting the proximal 15q have been described including supernumerary isodicentric 15, interstitial 15q duplication or 15q deletion [Schroer et al., 1998]. Their phenotypic patterns are almost similar, which include developmental delay, autistic or autistic-like behavior, moderate to profound intellectual disability, and epilepsy [Webb, 1994]. Expressive language is absent or very poor; it is often echolalic. Comprehension is very limited, contextual and is accompanied by the gesture [Battaglia, 2008].

To our knowledge, a coexistence of Williams syndrome and 15q duplication syndrome has not been previously described. Herein, we report the case of a girl with concurrent Williams syndrome and 15q duplication syndrome, who had an unusual pubertal course. She underwent treatment for CPP as a child and later on, during adolescence, presented with primary amenorrhea.

Case Report

A girl, 16 years and 9 months of age, with history of Williams syndrome, 15q duplication syndrome, and global developmental delay presented to the pediatric endocrine clinic with primary amenorrhea. She was full term, born small for gestational age with a birth weight of 1,956 g. She had previous history of precocious puberty (received leuprolide monthly injections from age 7–11

years), supraaortic stenosis (repaired), G-tube placement since 3 years of age for failure to gain weight, juvenile idiopathic scoliosis, slipped capital femoral epiphysis – status post screw fixation of the left hip, asthma, and developmental delay. She was not toilet trained and was nonverbal. No family history of early or delayed puberty or a similar syndrome or presentation was reported. The mother's menarche was at 14 years of age with regular periods; however, the father's pubertal details were not known. Midparental height was 157.3 cm (18th percentile).

On chart review, we found that our patient had been previously referred to a pediatric endocrine clinic at the age of 6 years and 8 months for early breast development. Her height at initial presentation then was 109.2 cm (9–25th percentile on Williams syndrome growth chart; the following percentiles also refer to this growth chart), weight was 24.1 kg (91st percentile), and BMI was 20.2 kg/m² (97th percentile). She was noted to have Tanner 2 breast and Tanner 2 pubic hair on physical examination. Baseline laboratory evaluation showed pubertal range gonadotropins [luteinizing hormone (LH) 0.3 mIU/ml, follicle stimulating hormone (FSH) 5.67 mIU/ml] and estradiol (36 pg/ml). Bone age assessment performed at chronological age of 6 years and 8 months was 7 years and 10 months with an SD of 9.64 months (within 2 SD of normal). The patient was lost to follow-up and returned back to the clinic a year later (at age 7 years and 9 months) when she was noted to have progression of pubertal development with Tanner 3 breast and Tanner 2 pubic hair. Her height then was 116.8 cm (25th percentile) and her weight was 30.3 kg (91st–98th percentile). Her growth velocity was 7 cm per year (reference 5–6 cm per year). MRI of the brain and pituitary showed mild prominence of the lateral and third ventricles with a well-defined area of cerebrospinal fluid in the left temporal lobe suggestive of an arachnoid cyst and a normal pituitary gland. She was started on monthly gonadotropin-releasing hormone analogue, leuprolide acetate treatment for pubertal suppression. She received leuprolide acetate 11.25 mg depot every month until 11 years of age. Gonadotropin levels and pubertal progression were suppressed while the patient was on leuprolide treatment. The treatment was stopped at age 11 years.

The patient was referred to the endocrine clinic again at the age of 16 years and 9 months for primary amenorrhea. Her mother denied the girl having any vaginal spotting, monthly abdominal cramps, excessive facial hair, acne, or being on any hormonal supplements. She denied frequent headaches or vomiting episodes, dry skin, hair loss, polyuria, polydipsia, change in weight, or temperature adjustment problems. She had been receiving both oral (mostly pureed) as well as G-tube feeding (pediasure 600 ml every 4 h). She could not swallow solid foods.

Anthropometric measurements at the age of 16 years and 9 months were: height 141.98 cm (9–25th percentile), weight 44.7 kg (9–25th percentile), and BMI 22.2 kg/m² (64th percentile). Physical examination was significant for dysmorphic facial features (hypertelorism, flat nasal bridge, prominent nasal tip, full lips, and macroglossia), poor dentition, midline incision scar on the chest, G-tube in place, Tanner 5 breast, and late Tanner 4 pubic hair. She was noted to have scoliosis and to walk with bent knees due to contractures. No hirsutism or acne was noted. No thyromegaly, no organomegaly, and no cardiac murmurs were noted. She was nonverbal, however was co-operative with the examination. Baseline laboratory tests revealed: estradiol 18.4 pg/ml (34–170 pg/ml), LH 3.33 mIU/ml (range: 1–18 mIU/ml), FSH 6.2 mIU/ml (4–13 mIU/ml). Repeat baseline laboratory tests obtained twice a few months

Table 1. Laboratory parameters during adolescence

	Reference range	Result	Interpretation
Estradiol, pg/ml	34–170	18.4	low for age
LH, mIU/ml	2–12	3.33	normal
FSH, mIU/ml	4–13	6.2	normal
IGF1, ng/ml	125–517	130	normal
IGFBP3, µg/l	2718–6495	5690	normal
TSH, µIU/ml	0.35–4.7	3.6	normal
FT4, ng/dl	0.71–1.85	1.11	normal
Total testosterone, ng/dl	6–82	7	normal
Prolactin, ng/ml	0–25	8.3	normal
ESR, mm/h	0–20	13	normal

ESR = Erythrocyte sedimentation rate; FT4 = free thyroxine; IGF1 = insulin-like growth factor; IGFBP3 = insulin-like growth factor-binding protein 3; TSH = thyroid-stimulating hormone.

later revealed similar results: estradiol 11.3 pg/ml, LH 3.32 mIU/ml, FSH 5.4 mIU/ml and estradiol 18.7 pg/ml, LH 2.48 mIU/ml, FSH 7.18 mIU/ml. The rest of the laboratory parameters including the prolactin level, insulin-like growth factor 1, insulin-like growth factor-binding protein 3, thyroid-stimulating hormone, free thyroxine, and total testosterone level were within normal limits for age and gender (table 1). A leuprolide stimulation test was performed and revealed low baseline estradiol with elevated post-stimulation LH, FSH, and estradiol levels (table 2).

Genetic testing was repeated due to the unavailability of documented prior genetic results. Karyotype revealed 47,XX,+mar (extra bisatellited marker chromosome of unknown origin in all metaphases). FISH for the supernumerary marker was consistent with partial trisomy/tetrasomy for proximal chromosome 15q (15p13q13). FISH using an ELN-specific probe demonstrated a deletion in the Williams syndrome critical region at 7q11.23.

Bone age was read as 16 years at chronological age of 16 years and 9 months and was within normal limits. Pelvic ultrasound revealed a hypoplastic uterus for age measuring $4.2 \times 1.8 \times 2.4$ cm. The endometrial stripe measured 2.3 mm; ovaries were not clearly identified here. MRI of the pelvis was performed which confirmed hypoplastic uterus and ovaries [uterus $3.7 \times 1.1 \times 2.7$ cm, right ovary $2 \times 1.1 \times 1.2$ cm (volume 1.3 cc), and left ovary $1.5 \times 1.3 \times 1.3$ cm (volume 1.4 cc)] with a thin endometrial lining (endometrium 0.4 cm) suggesting low estradiol levels.

Our patient underwent a progesterone challenge test without response. She was started on combined estrogen and progesterone replacement pills and has been having normal monthly menses since.

Discussion

Herein, we report the first case of Williams syndrome with coexisting 15q duplication syndrome. Our patient had clinical features of both syndromes. She had an unusual pubertal course with precocious puberty as a child

Table 2. Leuprolide stimulation test

	Baseline	1 h	2 h	18–24 h
LH, mIU/ml	5.06	21.54	30.39	19.59
FSH, mIU/ml	6.8	11.09	13.9	14.66
Estradiol, pg/ml	13.1	–	–	123.9

Low baseline estradiol for age with normal estradiol response to leuprolide stimulation test

and primary amenorrhea as an adolescent. She continued to have amenorrhea 6 years after discontinuing gonadotropin-releasing hormone analogue therapy. She had normal breast development and adrenarche changes; however, menarche was delayed.

Her facial features were consistent with Williams syndrome as well as the clinical features including supravalvular aortic stenosis, poor growth, and early puberty. The nonverbal behavior, which is in contrast to the friendly and hypersocial personality typical of Williams syndrome, was congruent to that described for 15q duplication syndromes. Williams syndrome patients are known to have mild to moderate intellectual disability with full scale IQ averaging 50–60 [Martens et al., 2008]. Young children with Williams syndrome are delayed in motor skill acquisition and in the achievement of language milestones. Developmental delays have been described in 15q duplication syndrome. Our patient had global developmental delays and was not toilet trained. The etiology of primary amenorrhea observed in our patient is unusual and cannot be completely explained by her genotype.

Table 3. Comparison of laboratory parameters at different ages

	6 years (initial presentation)	10 years (on leuprolide)	14 years (off leuprolide for 3 years)	16 years (off leuprolide for 5 years)
Estradiol, pg/ml	36	<32	8	18.4
LH, mIU/ml	0.3	<0.1	2	3.33
FSH, mIU/ml	5.67	1.01	5.37	6.2

Pubertal range values at age 6 years, suppression during leuprolide treatment, resumption of pubertal range levels at age 14 years, low levels for age and Tanner at age 16 years.

Williams syndrome is known to be associated with CPP [Scothorn and Butler, 1997; Cherniske et al., 1999; Douchi et al., 1999]. A study by Partsch et al. [2002], including 171 girls and women with Williams syndrome, showed that 93 of them had precocious puberty. Of 93 patients, 17 had CPP, and 5/17 were treated with gonadotropin-releasing hormone (GnRH) agonists. Our patient's presentation with CPP was consistent with the Williams syndrome phenotype. She received treatment with leuprolide (GnRH agonist) for 4 years, which successfully delayed her pubertal advancement.

CPP has been treated with GnRH agonists for years now. GnRH agonist therapy has been proven to be successful in delaying pubertal onset and improving final predicted adult height. Earlier, there were some reports of it tampering with the reproductive axis and its association with amenorrhea, hirsutism, polycystic ovary syndrome, metabolic syndrome, and decrease in bone mineral density. However, subsequent studies have reported its safety and efficacy for use in children and adolescents with CPP [Heger et al., 2006; Magiakou et al., 2010]. It is reported that the incidence of polycystic ovary syndrome in patients receiving GnRH agonist therapy does not differ from the general population [Heger et al., 2006]. The effects on bone mineral density are shown to be reversible after discontinuation of therapy [Magiakou et al., 2010], and no long-term reproductive side effects have been reported [Jay et al., 1992; Feuillan et al., 1999; Magiakou et al., 2010]. The mean onset of menses after terminating GnRH agonist therapy in girls has been reported to be 1.5 years (range 2–61 months). Hormones return to pubertal levels in most patients ~6 months after discontinuing therapy [Neely et al., 2010]. In our patient, the amenorrhea occurring 6 years after stopping leuprolide treatment appears less likely to be secondary to leuprolide treatment in light of the above evidences. Besides, she achieved normal development of secondary

sexual characteristics, which suggests normalization of the hormonal axis after GnRH agonist discontinuation for some time. However, there had to be some inciting event that led to hypogonadism and resulted in absence of menses. Table 3 summarizes the atypical variations in the hormonal levels of our patient going from childhood to puberty. The hypoplastic ovaries and uterus as well as the thin endometrium visualized on the sonogram indicate persistent and long-term absence of estrogen.

Duplications distal to 15q13 are rare and have been reported to be associated with hypogonadism. Herr et al. [1983] reported a 12-year-old boy with a de novo interstitial duplication of 15q14q21.1, who presented with scrotal hypoplasia and micropenis, short stature, seizure disorder, distinctive facial features, kyphosis and scoliosis, global developmental delay, and intellectual disability. Elçioglu et al. [1997] described a patient with hypogonadism, dysmorphic facial features, hypotonia, developmental delay, Marfan-like features and intellectual disability, who carried a de novo interstitial inverted duplication involving bands 15q13.3q21.3. Recently, Yuan et al. [2016] described an interstitial duplication of 15q15.3q21.1 in a 14-year-old boy with severe short stature, delayed bone age, hypogonadism, global developmental delay, and intellectual disability. A micropenis, small testes and low testosterone were detected in this patient. Yuan et al. [2016] speculated that duplication of the *EID1* gene may be responsible for the hypogonadism phenotype. *EID1* is known to be coexpressed with the steroidogenic factor-1 (SF-1), which plays a critical role in the adrenal and reproductive development and function. However, hypogonadism in duplications involving the proximal 15q11q13 regions, have not been reported. Therefore, it is not clear if the aberrations in the 15q chromosome have led to the hypogonadism observed in our patient.

At this point, the etiology of the hypogonadism in our patient is not completely understood, although the child-

hood-onset CPP was most likely part of the Williams syndrome phenotype. We currently are treating her with combined estrogen and progesterone replacement therapy to which she is responding well. We are hopeful that the uterine and ovarian volumes will improve with the hormonal stimulation and cyclic menstrual bleeding.

Conclusion

To our knowledge, a coexistence of Williams syndrome and 15q deletion syndrome has not yet been reported. It is unknown how the co-occurrence of these 2 syndromes would affect the phenotype of the patients.

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Statement of Ethics

Written informed consent was obtained from the parent prior to genetic testing and in accordance with the national ethics guidelines.

Disclosure Statement

The authors have nothing to disclose.