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Primary Amenorrhea and Absent Uterus in the 22q11.2 Deletion Syndrome

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Abstract

The classic clinical features in the 22q11.2 deletion syndrome are congenital heart defects, hypocalcemia, immunodeficiency, learning, speech, and behavioral difficulties. The phenotype is highly variable and continues to expand. We present two cases of absent uterus and unilateral renal agenesis in females with the 22q11.2 deletion. Clinicians caring for these adolescents should be aware of the possibility of renal anomalies and Mullerian agenesis. The diagnosis of 22q11.2 deletion may be considered in a female with Mullerian agenesis, particularly, in association with a history of learning difficulties and speech delay.

Keywords

22q11.2 deletion syndrome; Mullerian agenesis; vaginal agenesis; renal agenesis

INTRODUCTION

The 22q11.2 deletion syndrome, also referred to as DiGeorge, velocardiofacial and conotruncal anomaly face syndrome, is a common condition with an incidence of 1 in 4,500 to 1 in 7,100 live births [Tezenas Du Montcel et al., 1996; Botto et al., 2003; Oskarsdottir et al., 2004]. Typical clinical features include congenital heart defects, immunodeficiency, hypocalcemia, characteristic facial features, learning, speech, and behavioral difficulties. However, the findings are variable and the clinical spectrum is continuously expanding [McDonald-McGinn et al., 1999; Emanuel et al., 2001]. Here, we report two patients with the 22q11.2 deletion who had an absent uterus and unilateral renal agenesis.

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CLINICAL REPORTS

Patient 1 was born at term to a primigravida after an uncomplicated pregnancy. Her birth weight was 2,990 g. She walked at 18 months and had delays in emergence of language. She had febrile seizures at the age of 2. A renal sonogram performed following a bladder infection demonstrated a single kidney and absent uterus. A CT scan performed as part of the evaluation for a non-febrile seizure at age 13 years revealed basal ganglion calcification. Subsequently, hypoparathyroidism was diagnosed. Her serum calcium was 7.7 mg/dl, phosphorous 6.3, PTH 5.1 (12–65 pg/ml), 25-OH vitamin D3 30.7 and 1, 25-dihydroxy D3 36.7 (15.9–55.6 pg/ml). She was also noted to have an elevated HgA1c but a normal glucose tolerance test. Following this she was referred to genetics with a suspected diagnosis of Albright hereditary osteodystrophy (AHO). She was under the care of a neurologist for mood swings, oppositional behavior, and moderate attention problems that were treated with Concerta and Paxil. The family history is significant for a maternal cousin with a single kidney. On exam at 13 years, her weight was 81.3 kg (>97th centile), height was 157 cm (25th centile), and head circumference was 59 cm (98th centile). She was noted to have almond shaped eyes, a broad face, low hairline, normal appearing nose, lips mouth and uvula. She had thick helices and pinnae measured 4 cm bilaterally. The cardiac, respiratory, abdominal, back and genital examination were unremarkable. She had post-pubertal pubic hair. She did not have short broad hands or absent 4th or 5th metacarpals as seen in AHO. However, 22q11 deletion syndrome was considered due to the mild developmental delay, psychiatric symptoms, and the hypocalcaemia. Chromosome analysis revealed a normal female karyotype (46,XX) however, fluorescence in situ hybridization (FISH) studies showed a deletion of chromosome 22q11.2.

Patient 2 is a 19-year-old female, high school senior referred by her cardiologist because of bicuspid aortic valve, short stature, and primary amenorrhea to rule out Turner syndrome. She had a 1-year history of light-headedness, dizziness, and near syncope. Echocardiography revealed mild bicuspid aortic valve and mild aortic insufficiency and it was felt that her complaints were not cardiac in origin.

She was the 2,727 g, 48 cm product of a full-term pregnancy. Developmentally, she was reportedly about 6 months behind in achieving motor milestones, as compared to her two siblings, and spoke her first words at age 2. She was placed in a transitional first grade following kindergarten and since then she has been in a regular classroom setting. She reports having difficulty in math and science but has been accepted to college. Her past medical history is significant for bilateral inguinal hernias repaired at age 4 years. She had urethral strictures, which led to a urology workup. Sonographic examination demonstrated an absent right kidney and uterus. She went through normal puberty with breast development starting at age 11, but has never menstruated. Physical exam, when seen at age 19, showed a height of 147.9 cm, less than the 5th centile (50th centile for 11.5 years), head circumference of 53.6 cm (15th centile), normal breast development, normal axillary and pubic hair, no evidence of a webbed neck, and no cubitus valgus. She was, however, noted to have hooded eyelids with a slight upslant to the palpebral fissures, a high arched palate, and a bulbous nasal tip with a nasal depression. Based on these findings, short stature, and her school performance, a 22q11.2 deletion was suspected and this was confirmed by FISH. Cytogenetic studies showed a 46,XX karyotype.

DISCUSSION

Since the identification of the 22q11.2 deletion as the genetic etiology of velocardiofacial syndrome, and the conotruncal anomaly face syndrome, many cases of the DiGeorge anomaly, some cases of autosomal dominant Opitz G/BBB syndrome, we have come to appreciate the wide phenotypic variability of this condition [McDonald-McGinn et al., 1999; Emanuel et al., 2001]. In addition to the classic features, urinary tract anomalies are seen in one-third of patients

with the 22q11.2 deletion [McDonald-McGinn et al., 1999; Wu et al., 2002]. A range of renal anomalies have been described including renal agenesis, multicystic kidney, duplex kidney, renal cysts, and hydronephrosis. Unilateral renal agenesis, as described in our two patients, occurs in approximately 10% of patients, which is tenfold higher than the general population [Wu et al., 2002]. The combination of absent kidney and uterus has been previously reported in the 22q11.2 deletion syndrome. Devriendt et al. [1997] described a female fetus with Potter sequence secondary to unilateral renal agenesis and contralateral multicystic dysplasia. The fetus also had agenesis of the uterus and oviducts. A second case of absent uterus with bilateral agenesis of the fallopian tubes, Mullerian portion of the vagina, and absence of the right kidney, ureter, and trigone was reported in an autopsy series of 13 patients with the 22q11.2 deletion, 9 of whom were female [Huff et al., 2001]. We report on two additional patients in an effort to expand the 22q11.2 deletion phenotype to include absent Mullerian structures.

Mayer-Rokitansky-Kuster-Hauser (MRKH) anomaly or Mullerian aplasia results in primary amenorrhea due to congenital absence of the fallopian tubes, uterus, and proximal portion of the vagina. In some cases, the uterus may be rudimentary with a functional endometrium that can cause cyclical abdominal pain. The ovaries are normal and hence, secondary sexual development is normal. Mullerian aplasia occurs in 1/4,000–1/10,000 newborn females [Evans et al., 1981]. Mullerian anomalies are frequently associated with renal and skeletal anomalies. Both kidney and female internal genitalia develop from intermediate mesoderm. Several genes appear to be involved in Mullerian duct development including *PAX2*, *Wnt-4*, and *HOXA 9, 10, 11, 13* [MacLaughlin and Donahoe, 2004]. Mullerian aplasia can also occur as a result of mutation in the gene encoding hepatic transcription factor-2 (*TCF2*) [Lindner et al., 1999]. The genes within chromosome 22q11.2 responsible for the renal and Mullerian anomalies remain to be determined.

The prevalence of Mullerian anomalies in females with the 22q11.2 deletion is unknown. However, based on the previous reports and these two patients it is reasonable to consider Mullerian or uterine/vaginal agenesis as part of the spectrum of clinical features in this deletion syndrome. The diagnosis should be considered in a female patient with the 22q11.2 deletion who experiences primary amenorrhea. Examination of the external genitalia will reveal normal secondary sexual development with a vaginal dimple or small pouch. Pelvic and renal sonogram is recommended to assess the status of the kidneys, ovaries, and uterus. A pelvic MRI may be helpful to determine the extent of the genital anomalies and if there is functional endometrium present, particularly in the patient with cyclical lower abdominal or pelvic pain. In some cases, laparoscopy may be necessary to evaluate pelvic pain in these patients [Gell, 2003]. Psychological support may be needed and patients should be informed that a vagina can be created that will allow for a normal sex life.

Clinicians caring for children with a 22q11.2 deletion should remain mindful of the association with renal anomalies and Mullerian agenesis. Further, the 22q11.2 deletion syndrome may be considered in the differential diagnosis of Mullerian agenesis, especially in combination with a history of learning or speech difficulties.

References

- Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, Merritt RK, O'Leary LA, Wong LY, Elixson EM, Mahle WT, Campbell RM. A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics* 2003;112:101–107. [PubMed: 12837874]
- Devriendt K, Moerman P, Van Schoubroeck D, Vandenberghe K, Fryns JP. Chromosome 22q11 deletion presenting as the potter sequence. *J Med Genet* 1997;34:423–425. [PubMed: 9152843]
- Emanuel BS, McDonald-McGinn D, Saitta SC, Zackai EH. The 22q11.2 deletion syndrome. *Adv Pediatr* 2001;48:39–73. [PubMed: 11480765]

- Evans TN, Poland ML, Boving RL. Vaginal malformations. *Am J Obstet Gynecol* 1981;141:910–920. [PubMed: 7032301]
- Gell JS. Mullerian anomalies. *Semin Reprod Med* 2003;21:375–388. [PubMed: 14724770]
- Huff DS, McDonald-McGinn DM, Zackai EH. The first autopsy series in patients with a 22q11.2 deletion. *Am J Hum Genet* 2001;69:283.
- Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. *Hum Mol Genet* 1999;8:2001–2008. [PubMed: 10484768]
- MacLaughlin DT, Donahoe PK. Sex determination and differentiation. *N Engl J Med* 2004;350:367–378. [PubMed: 14736929]
- McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, Moss E, Solot C, Wang P, Jacobs I, Handler S, Knightly C, Heher K, Wilson M, Ming JE, Grace K, Driscoll D, Pasquariello P, Randall P, Larossa D, Emanuel BS, Zackai EH. The Philadelphia story: The 22q11.2 deletion: Report on 250 patients. *Genet Couns* 1999;10:11–24. [PubMed: 10191425]
- Oskarsdottir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: A population-based study in western Sweden. *Arch Dis Child* 2004;89:148–151. [PubMed: 14736631]
- Tezenas Du Montcel S, Mendizabai H, Ayme S, Levy A, Philip N. Prevalence of 22q11 microdeletion. *J Med Genet* 1996;33:719. [PubMed: 8863171]
- Wu HY, Rusnack SL, Bellah RD, Plachter N, McDonald-McGinn DM, Zackai EH, Canning DA. Genitourinary malformations in chromosome 22q11.2 deletion. *J Urol* 2002;168:2564–2565. [PubMed: 12441983]