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Consideration of VACTERL association in patients with trisomy

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Introduction

The presence of VACTERL association may be diagnosed in patients with a combination of the following congenital malformations: **V**ertebral defects, **A**nal atresia, **C**ardiac malformations, **T**racheo-**E**sophageal fistula, **R**enal anomalies, and **L**imb abnormalities. Since its first description in 1972, the definition has continued to shift, and in current practice, the criteria for diagnosis may differ between clinicians, but most clinicians require the presence of at least three component features without clear evidence for an alternate, overlapping diagnosis, of which there are many (these include Fanconi anemia, Townes-Brocks syndrome, CHARGE syndrome, and Pallister-Hall syndrome). Estimates of incidence are challenging, but several large epidemiological studies show an incidence of VACTERL association of approximately 1 in 20,000 to 35,000 infants (Botto *et al.*, 1997; Rittler *et al.*, 1997).

Patients with Down syndrome have congenital malformations much more frequently than in the general population, and approximately 40% of patients with Down syndrome have at least one congenital malformation. However, the presence of multiple malformations in patients with Down syndrome is less common (Cleves *et al.*, 2007). We present two patients with confirmed trisomy 21 for whom a second diagnosis of VACTERL association was also considered. These patients participated in our National Human Genome Research Institute IRB-approved research protocol on VACTERL association, with appropriate consent obtained from all participants.

Clinical Reports

Patient 1 was an eighteen year-old female with trisomy 21 diagnosed in infancy secondary to facial features consistent with Down syndrome. Features which raised the possibility of

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VACTERL association included multiple vertebral/spinal anomalies (spina bifida occulta at C5, deformity of the body of C2 with partial fusion deformity with C3, and mild scoliosis of the cervical, thoracic, and lumbar spine, and a tethered cord) (Fig. 1b–c). She was diagnosed as a neonate with a low imperforate anus, which was initially repaired on the first day of life. An echocardiogram in infancy showed the presence of a ventricular septal defect, atrial septal defect, and a patent foramen ovale, though these cardiac malformations did not require surgery and were not present on echocardiogram performed at 18 years of age. She did not have evidence for a tracheo-esophageal fistula. Physical examination of the limbs showed no abnormalities except those well-known to be associated with Down syndrome, but X-ray of the limbs revealed minimal bowing deformities of the radius and ulna bilaterally (Fig. 1a). Abdominal ultrasound showed no renal or other anomalies, and serum and urine screening showed no evidence for renal dysfunction, though she did have a history of neurogenic bladder and mild vesicoureteral reflux, which were likely multifactorial and related to her congenital malformations. She had no other major malformations. Physical examination revealed no dysmorphic findings other than those classically associated with Down syndrome. The patient had a healthy younger sibling, and there was no known history of similar medical issues or features of VACTERL in any relatives. A high-resolution karyotype performed on peripheral blood did not show any anomalies other than trisomy 21. Chromosomal breakage studies (DEB assay) to test for Fanconi anemia, performed because of the subtle radial anomalies, were normal. The patient was overall doing very well medically, and was soon to complete secondary school, with plans for employment after graduation.

Patient 2 was a six-week old female infant born prematurely at 32 weeks gestation to a 40 year-old G2P0010 mother with a history of one previous spontaneous abortion very early in gestation, though further details were unknown and pathological examination was not performed. Trisomy 21 was diagnosed prenatally via amniocentesis, but high resolution chromosome analysis was otherwise normal. Prenatal imaging, by ultrasound, echocardiogram, and fetal MRI, revealed a tethered spinal cord with an intraspinal lipoma in conjunction with a sacral vertebral defect, an atrioventricular (AV) canal type cardiac malformation, an omphalocele, and exstrophy of the bladder. Anal atresia was noted immediately after birth. Imaging obtained after delivery further demonstrated that the patient's vertebral anomalies included (by MRI) mild segmentation anomalies of T8–T9 and T10–T11, as well as sacral hypogenesis (Fig. 1d). Postnatal echocardiogram showed an unbalanced AV defect with a hypoplastic left heart, especially posteriorly, as well as a large patent ductus arteriosus. Abdominal ultrasound showed mild separation of the right renal pelvis, but no additional renal anomalies. She additionally had an omphalocele and cloacal exstrophy (including the ileum and bladder), with an absent urethra. A postnatal brain MRI was normal with the exception of mild pontocerebellar hypoplasia and an immature sulcation pattern, even for corrected gestational age, with a suggestion of mild frontoparietal and temporal lobe hypoplasia. Physical examination revealed features consistent with Down syndrome but no additional dysmorphic features other than those directly related to her structural organ anomalies.

A diverting colostomy was performed on the first day of life, but further surgical interventions were not attempted, and the patient passed away at two months of age secondary to multiorgan failure related to acidosis and poor perfusion. Autopsy confirmed the above findings, and additionally showed the presence of bilateral adrenal hypoplasia. There was no family history of similar medical issues.

Discussion

Patient 1 had evidence for three component features of VACTERL association (vertebral anomalies, anal atresia, and a cardiac malformation), and also had mild radial and ulnar bowing.

This latter feature may be simply a variant associated with Down syndrome rather than a true limb anomaly. Patient 2 had the same three component features of VACTERL association (vertebral anomalies, anal atresia, and a cardiac malformation) as well as omphalocele and cloacal exostrophy. Genitourinary anomalies are not one of the defining component features of VACTERL association. However, this type of malformation is frequent in patients with VACTERL association, and many consider it to be an extension of the component features, both because of statistical prevalence and because the developmental biology of the hindgut is closely tied to that of the genitourinary system (Rittler *et al.*, 1997; Solomon *et al.*, 2010).

It is difficult to judge whether these patients' features are simply a severe manifestation of Trisomy 21 or if a second condition such as VACTERL association is superimposed. As Down syndrome occurs at a frequency of approximately 1 in 1,000 livebirths, it is to be expected that some patients with Down syndrome would have a second, co-incident condition. And while major malformations are common in patients with Down syndrome, the presence of multiple malformations is relatively rare. Only 0.20% of patients with Down syndrome have major anomalies affecting three organs (as with patient 1), and only 0.02% have anomalies affecting four or more organs (as in patient 2) (Cleves *et al.*, 2007) (Table 1). Finally, while both patients were referred to our research study because of the possible presence of VACTERL association, it is entirely possible that they might have an alternate, overlapping diagnosis.

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References

- Botto LD, Khoury MJ, Mastroiacovo P, Castilla EE, Moore CA, Skjaerven R, Mutchinick OM, Borman B, Cocchi G, Czeizel AE, Goujard J, Irgens LM, Lancaster PA, Martínez-Frías ML, Merlob P, Ruusinen A, Stoll C, Sumiyoshi Y. The spectrum of congenital anomalies of the VATER association: an international study. *Am J Med Genet* 1997;71:8–15. [PubMed: 9215761]
- Cleves MA, Hobbs CA, Cleves PA, Tilford JM, Bird TM, Robbins JM. Congenital defects among liveborn infants with Down syndrome. *Birth Defects Res A Clin Mol Teratol* 2007;79:657–663. [PubMed: 17696161]
- Keeling JW, Hansen BF, Kjaer I. Pattern of malformations in the axial skeleton in human trisomy 21 fetuses. *Am J Med Genet* 1997;68:466–471. [PubMed: 9021023]
- Milbrandt TA, Johnston CE II. Down syndrome and scoliosis: a review of a 50-year experience at one institution. *Spine* 2005;30:2051–2055. [PubMed: 16166894]
- Rittler M, Paz JE, Castilla EE. VATERL: an epidemiologic analysis of risk factors. *Am J Med Genet* 1997;73:162–169. [PubMed: 9409866]
- Solomon BD, Pineda-Alvarez DE, Raam MS, Cummings DA. Evidence for inheritance in patients with VACTERL association. *Hum Genet*. 2010 [Epub ahead of print].

Fig. 1.

a: Upper extremity X-rays of patient 1 shows mild radial and ulnar bowing bilaterally, prompting testing for Fanconi anemia; b: Cervical vertebral anomalies in patient 1 included C5 spina bifida occulta (arrow indicates the C5 level), deformity of the body of C2 with partial fusion deformity with C3; c: mild cervical, thoracic, and lumbar scoliosis in patient 1; d: Spinal MRI of patient 2, demonstrating the intraspinal lipoma (arrow) at the level of the sacral vertebral anomalies.

Table 1

Prevalence of major structural anomalies observed in the patients reported here among patients with Down syndrome.

Feature	Prevalence among patients with Down syndrome (%)	Reference
Cervical vertebral anomalies (Patient 1)	14/31 (45%)	Keeling <i>et al.</i> , 1997*
Thoracic vertebral anomalies (Patient 2)	4/31 (13%)	Keeling <i>et al.</i> , 1997
Lumbosacral vertebral anomalies (Patient 2)	8/31 (26%)	Keeling <i>et al.</i> , 1997
Scoliosis (Patient 1)	33/379 (8.7%)	Milbrandt and Johnston, 2005
Anal atresia (Patients 1 & 2)	390/43,463 (0.90%)	Cleves <i>et al.</i> , 2007
All cardiac defects (Patients 1 & 2)	15,885/43,463 (36.5%)	Cleves <i>et al.</i> , 2007
AV canal (Patient 2)	4,671/43,463 (10.7%)	Cleves <i>et al.</i> , 2007
VSD (Patient 1)	5,820/43,463 (13.4%)	Cleves <i>et al.</i> , 2007
ASD (Patient 1)	7,756/43,463 (17.8%)	Cleves <i>et al.</i> , 2007
GU anomalies (Patient 2)	991/43,463 (2.3%)	Cleves <i>et al.</i> , 2007 [†]
Omphalocele (Patient 2)	23/43,463 (0.052%)	Cleves <i>et al.</i> , 2007

* This study described results from pathological and radiological examination of deceased fetuses with trisomy 21, rather than liveborn patients. This article specified the frequency of anomalies affecting each individual region of the spine, rather than the overall prevalence of vertebral anomalies.

[†] In this study, no patients were reported with Down syndrome and bladder exstrophy, as was observed in patient 2.

ASD: Atrial Septal Defect AV: Atrioventricular; GU: Genitourinary; VSD: Ventricular Septal Defect.