J Neurosurg Pediatrics 6:177–182, 2010

Prevalence of tethered spinal cord in infants with VACTERL

Clinical article

Brent R. O'Neill, M.D.,[1] Alexander K. Yu, M.D.,[2] and Elizabeth C. Tyler-Kabara, M.D., Ph.D.[3]

[1]Department of Neurosurgery, University of Washington, Seattle, Washington; [2]Department of Neurosurgery, Allegheny General Hospital; and [3]Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Object. The term VACTERL represents a nonrandom association of birth defects including vertebral malformations, anal atresia, cardiac anomalies, tracheoesophageal fistulas (TEFs), renal anomalies, and limb malformations. Clinical experience and a few published case series suggest that a tethered spinal cord (TSC) occurs commonly in children with VACTERL, but to date, no study has defined the prevalence of TSC in patients with VACTERL. Such information would guide decisions about the appropriateness of screening spinal imaging.

Methods. The authors reviewed the charts of all patients discharged from the neonatal intensive care unit at Children's Hospital Pittsburgh in the past 14 years with the diagnosis of VACTERL, TEF, or anal atresia. During that period, the authors' protocol has been to use spinal ultrasound to screen this population for TSC. The charts were reviewed for the presence of a TSC requiring surgery and for the features of VACTERL.

Results. Thirty-three patients with VACTERL and adequate spinal imaging studies were identified. In 13 (39%) of these, a TSC requiring surgery was identified. Among patients without VACTERL, the incidence of TSC was 7.9% in those with anal atresia and 2.4% in those with TEF. False-negative ultrasounds were identified in 21.4% of patients with TSC.

Conclusions. Children with VACTERL should undergo MR imaging screening for TSC. In infants with anal atresia without VACTERL, the incidence of TSC is much lower than in those with VACTERL.
(DOI: 10.3171/2010.5.PEDS09428)

Key Words • tethered spinal cord • spinal lipoma • VACTERL • imperforate anus • occult spina bifida

Vertebral anomalies (V), anal or duodenal atresia (A), cardiac defects (C), tracheoesophageal fistula (TE), renal anomalies (R), and limb malformations (L) occur together in the congenital association termed VACTERL. This association was originally described in 1973 with the acronym VATER[18] in which the R signified both renal and radial (the most common limb defect) abnormalities, but frequent cardiac abnormalities observed in these patients led to later expansion of the acronym to VACTERL.[3]

The underlying cause of this association of birth defects has potentially been linked to the Sonic hedgehog signaling pathway.[12,21] This observation arose in studying a mouse model engineered with deletions of the *Gli2* and *Gli3 Shh* transcription genes. Mice with these genes knocked out have birth defects similar to those in the VACTERL spectrum. While this murine model offers a platform for new study of the syndrome, VACTERL has not been linked to a single genetic event and does not follow Mendelian inheritance patterns. The cause in humans appears instead to be multifactorial with significant environmental influence.[12]

Virtually all patients in whom VACTERL is eventually diagnosed will be admitted to an intensive care setting in the neonatal period due to the presence of an imperforate anus or TEF. Early admission to a critical care unit allows an opportunity to screen these infants for associated anomalies in the VACTERL spectrum and to treat prophylactically when appropriate.

Tethered spinal cord, a subcategory of occult spinal dysraphism (OSD), refers to a myriad of developmental intraspinal anomalies that bind the distal spinal cord low

Abbreviations used in this paper: OSD = occult spinal dysraphism; TEF = tracheoesophageal fistula; TSC = tethered spinal cord.

in the bony spinal canal, thereby applying tension to the cord as the bony canal grows faster than the neural tissue. These lesions include thickened filum terminale, filum terminale lipoma, dermal sinus, lipomyelomeningocele, and split cord malformations. Cutaneous markers such as dimples, nevi, hemangiomas, tufts of hair, and dermal sinuses frequently signal the presence of a TSC. A low-lying conus medullaris often accompanies OSD, providing further evidence of abnormal tension on and stretching of the distal spinal cord.

Tethered cord syndrome is the clinical manifestation of OSD. Bowel and bladder dysfunctions are the most common characteristics, but back pain, leg pain, motor and sensory disturbance of the lower extremities, scoliosis, and foot deformities may also be present.[2,14,20] Once a child presents with incontinence and orthopedic deformities, release of the tethered cord should halt progression, but the procedure is unlikely to reverse the deficits. The likelihood of such deficits developing from many of the milder forms of tethering (such as thickened filum and filum lipoma) is not known.

While good data on the natural history of infants with filum terminale lipoma and/or low-lying spinal cord is not known, prophylactic detethering surgery is undertaken in many of these infants in the hope of preventing irreversible deficits.[14,19] Early detection of a lesion is important to guide discussion of prophylactic detethering surgery or monitoring for early detection of neurological decline. Early symptoms of the tethered cord syndrome may be more difficult to properly recognize in infants with VACTERL because many have an imperforate anus that requires perineal surgery or congenital renal or urogenital anomalies.

Methods

After approval from the Children's Hospital of Pittsburgh Institutional Review Board, the neonatal intensive care unit discharge database from 1995 to 2008 was searched for ICD-9 codes 759.89 (congenital malformation syndromes affecting multiple systems including such diagnoses as VACTERL, CHARGE [Coloboma of the eye, Heart defects, Atresia of the nasal choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness], Fanconi anemia, and so on), 750.3 (tracheoesophageal fistula), and 751.2 (anal atresia).

During the period of this study, it has been the policy of the Children's Hospital Pittsburgh to screen all neonates with VACTERL, TEF, or imperforate anus with echocardiography, renal ultrasound, and spinal ultrasound. Abnormal spinal ultrasound results are followed up with MR imaging. In a few instances, spinal MR imaging was performed in the neonatal period for other reasons (for example, deformity). Spinal ultrasound studies were not obtained in some of these cases.

Patients in whom spinal ultrasound or MR imaging studies had not been obtained were excluded from this analysis to eliminate the sizable group with non-VACTERL congenital malformation syndromes.

Charts of the remaining patients were reviewed to confirm or exclude the diagnosis of VACTERL as strictly defined by Källén and colleagues.[10] The diagnosis of VACTERL was confirmed in children with anomalies in 3 or more of the categories defined in Table 1.

Spinal imaging studies were reviewed for all children. Neurosurgical consultations and neurosurgical operative details were likewise reviewed.

Results

In the past 14 years, the diagnostic codes for congenital malformation syndromes affecting multiple systems (VACTERL included), TEF, and anal atresia were ascribed to 239 patients discharged from the Pittsburgh Children's Hospital neonatal intensive care. In 135 of these patients, some form of spinal imaging had been performed. Their charts were reviewed. The remainder we presume had DiGeorge syndrome, Fanconi anemia, or other congenital malformation syndromes affecting multiple systems. In 23 children with spinal imaging we found, on chart review, multiple congenital malformation syndromes separate from TEF, anal atresia, and VACTERL. These cases were excluded, leaving 112 in the final analysis. Thirty-six patients met the criteria for VACTERL, as defined in

TABLE 1: Features of VACTERL*

Category
vertebral
hemivertebrae
butterfly vertebrae
fused segments
extra segments
atresias
anal atresia
duodenal atresia
cardiac
atrial septal defect (excluding PFO)
ventricular septal defect
dextrocardia
tetralogy of Fallot
aortic coarctation
duplicated aortic arch
tracheoesophageal
tracheoesophageal fistula
esophageal atresia
renal
horseshoe kidney
solitary kidney (agenesis)
dysplastic kidney
ureteropelvic obstruction
hypospadias
limb
absent radius
deformed radius
polydactyly
oligodactyly

* Abnormalities in 3 or more of the categories constitute a diagnosis of VACTERL. Abbreviation: PFO = patent foramen ovale.

Table 1. Among those without VACTERL, 38 had anal atresia, and another 38 had TEFs.

Among the subset with VACTERL, 3 patients were excluded from analysis because imaging studies were inadequate. All had low-lying conus medullaris on ultrasound but never underwent MR imaging. In 2 cases, the children died of cardiac malformations prior to discharge from the neonatal intensive care unit and in the third the patient was lost to follow-up before the recommended MR imaging was conducted.

Thirteen (39%) of the 33 patients with VACTERL had a TSC requiring surgery depicted on MR imaging (images from representative cases are shown in Figs. 1–3, and a complete list of cases appears in Table 2). Twelve of these patients underwent surgical detethering surgery while one was lost to follow-up prior to his surgery date. One patient had a lipomyelomeningocele, 8 had filum terminale lipomas, and 6 had syringes. Only 2 patients had a conus medullaris at or above the L2–3 level; in both of these cases the filum terminale lipomas were sizable.

Only 8 in the nonsurgical group underwent MR imaging. Magnetic resonance imaging revealed normal spinal cord anatomy in 3, borderline low conus medullaris in 2, a tiny filum terminale syrinx in 2, and a blunted conus medullaris in 1.

Among the children with VACTERL, all of those with TSC had vertebral anomalies, compared with 50% in the non-TSC group. Those with tethered cord were also more likely to have anal atresia and renal anomalies than VACTERL patients without TSC (Table 3). They also tended to have more features of VACTERL, with 62% having more than 3 features compared with 18% of those in the non-TSC group. Those with TSC were less likely to have TEF and cardiac abnormalities, whereas the 2 groups were almost identical in frequency of limb malformations.

Among the 38 non-VACTERL patients with anal atresia, 3 (7.9%) had a TSC requiring surgery; 2 had 1 associated VACTERL feature (ectopic kidney with ambiguous

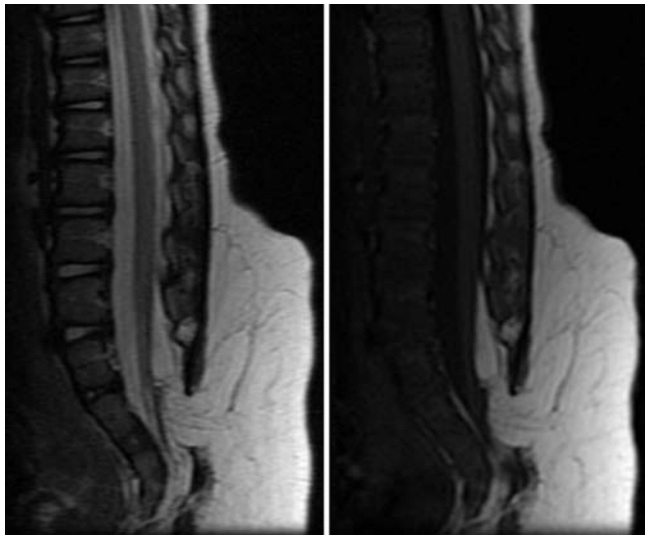

Fig. 2. Sagittal T2-weighted **(left)** and T1-weighted **(right)** MR images revealing a lipomyelomeningocele tethering the conus at S-2 in an infant with extra vertebral segments, anal atresia, absent kidney, hypospadias, and absent radius.

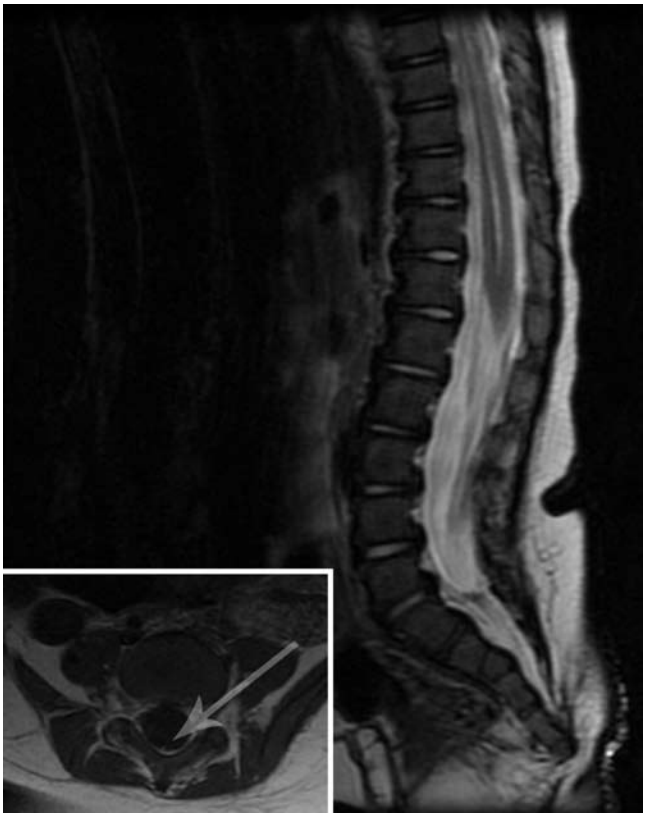

Fig. 1. Sagittal MR image obtained in a patient with anal atresia, absent thumb, and multiple vertebral anomalies including butterfly vertebrae, fused segments, and extra segments. The image shows the conus to end at the fourth of 8 lumbar vertebral bodies, an extensive syrinx, and a dorsally displaced, fatty filum (demonstrated by the *arrow* on the T1-weighted axial image **[inset]**).

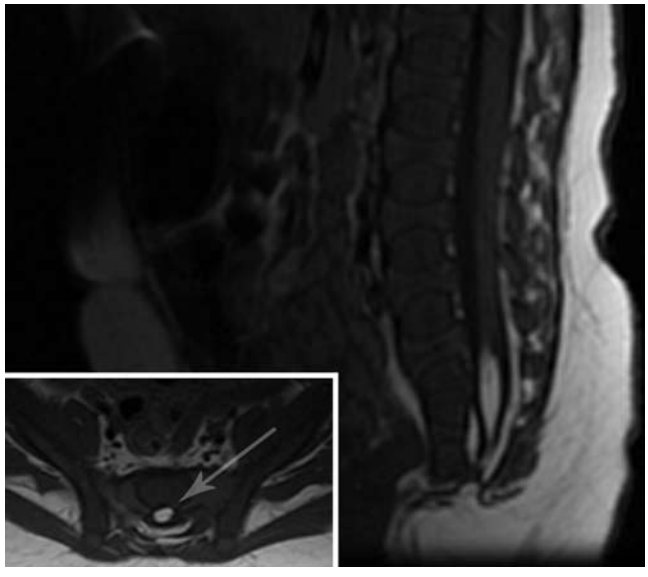

Fig. 3. Sagittal T1-weighted MR image acquired in an infant with anal atresia, tracheoesophageal fistula, and vertebral anomalies, showing the conus ending at L-5 in a sizable filum lipoma (*arrow* in the axial image **[inset]**). The upper sacral segments are fused while the lower segments are absent.

TABLE 2: Details of all 17 patients with TSC requiring surgery, including ultrasound findings and associated anomalies in the VACTERL spectrum*

Case No.	VACTERL	Spinal Cord Pathology	Ultrasound Findings	Associated VACTERL Anomalies
1	yes	L-4 conus	L-4 conus	6 lumbar, 14 thoracic vertebral bodies, anal atresia, ectopic kidney
2	yes	L-4 conus (of 8), filum lipoma, syrinx	normal	butterfly, fused, extra vertebral segments, anal atresia, renal cysts, absent thumb
3	yes	L4–5 conus	L2–3 conus	fused vertebral bodies, anal atresia, VSD, absent kidney
4	yes	L-3 conus, filum lipoma	not performed	13 ribs, malformed sacrum, anal atresia, TEF, ectopic kidney, hydronephrosis, hypospadias
5	yes	filum lipoma	normal	hemivertebrae, anal atresia, horseshoe kidney, ambiguous genitalia, club foot
6	yes	L-5 conus, filum lipoma, syrinx	L-5 conus, filum lipoma, syrinx	fused ribs & sacral segments, anal atresia, TEF
7	yes	L-3 conus, filum lipoma, holocord syrinx	syrinx	13 ribs, fused segment, anal atresia, VSD, TEF, horseshoe kidney
8	yes	L-4 conus	L-4 conus	extra segments, hemivertebrae, anal atresia, fused kidneys, hydronephrosis
9	yes	L2–3 conus, filum lipoma, syrinx	thick filum	sacral deformation, anal atresia, solitary ectopic kidney
10	yes	L-4 conus	not performed	hemivertebrae, rib anomalies, anal atresia, horseshoe kidney
11	yes	L2–3 conus (of 6), thick filum	L-3 conus	absent superior vena cava, TEF, renal ectasia, extra vertebral segments
12	yes	S-2 conus, lipomyelomeningocele	lipoma, suggestion of tether	extra vertebral segments, anal atresia, absent kidney, hypospadias, absent radius
13	yes	L3–4 conus (of 6), filum lipoma	thick filum	fused vertebral segments, ASD, TEF, hemibladder/phallus/scrotum
14	no	L5–S1 conus, thick filum	not performed	TEF, fused kidneys, hydronephrosis
15	no	L3–4 conus, filum lipoma	L3–4 conus, filum lipoma	anal atresia
16	no	L-4 conus, filum lipoma	L-4 conus	anal atresia, ectopic kidney, hydronephrosis
17	no	L-3 conus, filum lipoma, syrinx	normal	anal atresia, tetralogy of Fallot, VSD

* ASD = atrial septal defect; VSD = ventricular septal defect.

genitalia in one and tetralogy of Fallot with a ventricular septal defect in the other). In all, 16 (42%) of the 38 infants in the anal atresia group had an associated birth defect from the VACTERL spectrum. These were nearly evenly divided between vertebral (5 patients), cardiac (5 patients), and renal (6 patients) defects. No patients in this group had limb anomalies.

Thirty-eight of the non-VACTERL patients had tracheoesophageal fistulas. Only 1 (2.6%) of these 38 patients had TSC. This child had an associated renal anomaly in the form of fused kidneys with hydronephrosis. In this group, 14 of the 38 patients had 1 associated malformation in the VACTERL spectrum, a prevalence of 36.8%. Cardiac anomalies were the most common (7 patients), and this was followed by renal (4 patients) and vertebral (1 patient) defects.

Seventy-four of the 76 non-VACTERL patients underwent screening ultrasound, while only 13 patients (10 with anal atresia infants and 3 with TEF) underwent MR imaging.

Twenty-two of the patients with VACTERL underwent MR imaging. Two of these had false-negative ultrasound results, 1 had a false-positive ultrasound result, and 4 did not undergo ultrasound.

Of those in whom MR imaging documented a tethered cord, 3 had ultrasound studies that were interpreted as normal, giving a 21.4% false-negative rate for screening ultrasound (14 of the 17 patients with OSD underwent

TABLE 3: Comparison of VACTERL features between VACTERL patients with and without TSC

VACTERL Feature	No. of Patients (%)	
	TSC	Normal Ultrasound
no. of patients	13 (39) of 33	20 (61) of 33
vertebral	13 (100)	10 (50)
atresia	11 (85)	12 (60)
cardiac	3 (23)	11 (55)
tracheoesophageal	5 (38)	12 (60)
renal	12 (92)	12 (60)
limb	4 (31)	7 (35)
no. of features		
exactly 5	1 (8)	0
exactly 4	7 (54)	6 (30)
exactly 3	5 (38)	14 (70)

ultrasound). One of these patients had a normal-level conus medullaris with a filum terminale lipoma; 1 had a filum terminale lipoma, syrinx, and conus at L-4 of 8 lumbar segments; and 1 had a fatty filum terminale, syrinx, and conus ending at L-3.

Discussion

In the present study we found a 39% incidence of TSC requiring surgery when patients with VACTERL underwent neonatal ultrasound screening. This study is the first of which we are aware to report the results of universal screening for tethered cord in the VACTERL population.

There were some strong associations of tethered cord with certain VACTERL features in our population. Those with a tethered cord were more likely to have vertebral (100% vs 50%) and renal (92% vs 60%) malformations than those without a tethered cord. The universal presence of vertebral anomalies in the patients with a tethered cord may point to a common embryological misstep and suggests that screening spine radiography may be useful in excluding the possibility of underlying TSC. More data are needed to confirm this association.

Infants with VACTERL and TSC were less likely than those without TSC to have cardiac anomalies (23% vs 55%, respectively) and TEF (38% vs 50%). Neither of these associations excludes the possibility of spinal cord tethering, and we believe that all children with VACTERL deserve screening.

The protocol at our institution has been to conduct spinal ultrasound screening in all children with VACTERL, anal atresia, or TEF. In our chart review we documented a 21% false-negative rate for spinal ultrasound, but only a few of the more than 75 patients with normal ultrasound results underwent MR imaging, likely biasing the false-negative rate.

Evaluation of the accuracy of spinal ultrasound in detecting OSD and spinal cord tethering has not been fully assessed, but some reports have found complete correlation of the 2 modalities in only 40% of infants.[9] Further study of this modality is warranted, particularly in populations with a high prevalence of TSC such as VACTERL.

A number of publications have reported TSC in patients with VACTERL.[5,11,13,17,23] Chestnut and colleagues[5] reported on 6 surgical cases that presented over a 5-year period. Three of these presented with symptoms while the remaining 3 were identified in infancy after work-up for cutaneous markers.

Warf and associates[23] added 2 cases of VATER in a series of patients with anorectal malformations and TSC.

Kuo et al.[13] reported on 9 nonconsecutive patients with VACTERL who underwent lumbar MR imaging. Seven of these had a tethered cord, an incidence of 77.8%; however, the authors do not comment on how the patients in the series were selected for MR imaging evaluation. The high incidence may reflect some selection of who to screen in their VACTERL population, or it may result from the use of MR imaging as the screening modality (a more sensitive test than ultrasound).[9]

A larger body of literature addresses the association between anorectal malformations and spinal cord tethering. The reported incidence ranges from 8% to 36%.[1,4,6–8,15,16,22]

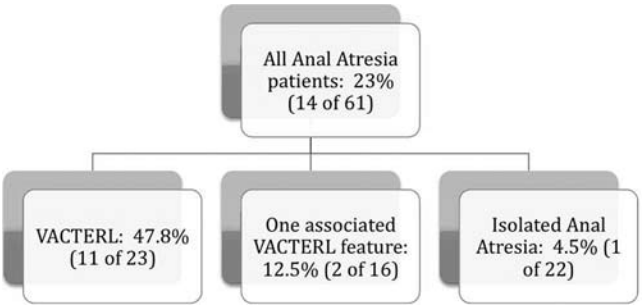

Fig. 4. Prevalence of TSC in patients with anal atresia.

Golonka and colleagues[7] reported one of the largest series in which MR imaging was used to routinely screen for infants with anal atresia. They found that 34.9% of their patients had a TSC. The authors noted a frequent association with vertebral anomalies, but no author studying anal atresia and TSC has commented on the association with VACTERL.

In the present study, 23% of infants with anal atresia had TSC; however, in those without VACTERL, the incidence was 7.9%, lower than any other report of prophylactically screened patients with anal atresia. The incidence was even lower (4.5%) in those without any VACTERL features (Fig. 4). Future studies of the association between anal atresia and TSC should include the association of VACTERL features.

Conclusions

Thirty-nine percent of patients with VACTERL were found to have TSC when screened as neonates with ultrasound. Three false-negative ultrasounds were identified among our 14 patients with TSC who underwent this imaging modality. Given the potential for insidious and often irreversible neurological deficits caused by untreated spinal cord tethering, we believe that routine screening is mandatory for children with VACTERL. The improved sensitivity of MR imaging compared with ultrasound probably justifies the increased cost and small risk of sedation-related morbidity. Although prospective study is warranted, we would nonetheless recommend routine MR imaging screening for all patients with VACTERL.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: O'Neill, Tyler-Kabara. Acquisition of data: O'Neill, Yu. Analysis and interpretation of data: O'Neill. Drafting the article: O'Neill. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: O'Neill, Tyler-Kabara. Administrative/technical/material support: Yu. Study supervision: Tyler-Kabara.

References

1. Appignani BA, Jaramillo D, Barnes PD, Poussaint TY: Dysraphic myelodysplasias associated with urogenital and ano-

rectal anomalies: prevalence and types seen with MR imaging. **AJR Am J Roentgenol 163:**1199–1203, 1994
2. Bao N, Chen ZH, Gu S, Chen QM, Jin HM, Shi CR: Tight filum terminale syndrome in children: analysis based on positioning of the conus and absence or presence of lumbosacral lipoma. **Childs Nerv Syst 23:**1129–1134, 2007
3. Botto LD, Khoury MJ, Mastroiacovo P, Castilla EE, Moore CA, Skjaerven R, et al: The spectrum of congenital anomalies of the VATER association: an international study. **Am J Med Genet 71:**8–15, 1997
4. Carson JA, Barnes PD, Tunell WP, Smith EI, Jolley SG: Imperforate anus: the neurologic implication of sacral abnormalities. **J Pediatr Surg 19:**838–842, 1984
5. Chestnut R, James HE, Jones KL: The Vater association and spinal dysraphia. **Pediatr Neurosurg 18:**144–148, 1992
6. Davidoff AM, Thompson CV, Grimm JM, Shorter NA, Filston HC, Oakes WJ: Occult spinal dysraphism in patients with anal agenesis. **J Pediatr Surg 26:**1001–1005, 1991
7. Golonka NR, Haga LJ, Keating RP, Eichelberger MR, Gilbert JC, Hartman GE, et al: Routine MRI evaluation of low imperforate anus reveals unexpected high incidence of tethered spinal cord. **J Pediatr Surg 37:**966–969, 2002
8. Heij HA, Nievelstein RAJ, de Zwart I, Verbeeten BW, Valk J, Vos A: Abnormal anatomy of the lumbosacral region imaged by magnetic resonance in children with anorectal malformations. **Arch Dis Child 74:**441–444, 1996
9. Hughes JA, De Bruyn R, Patel K, Thompson D: Evaluation of spinal ultrasound in spinal dysraphism. **Clin Radiol 58:**227–233, 2003
10. Källén K, Mastroiacovo P, Castilla EE, Robert E, Källén B: VATER non-random association of congenital malformations: study based on data from four malformation registers. **Am J Med Genet 101:**26–32, 2001
11. Keckler SJ, St Peter SD, Valusek PA, Tsao K, Snyder CL, Holcomb GW III, et al: VACTERL anomalies in patients with esophageal atresia: an updated delineation of the spectrum and review of the literature. **Pediatr Surg Int 23:**309–313, 2007
12. Kim PCW, Mo R, Hui CC: Murine models of VACTERL syndrome: role of sonic hedgehog signaling pathway. **J Pediatr Surg 36:**381–384, 2001
13. Kuo MF, Tsai Y, Hsu WM, Chen RS, Tu YK, Wang HS: Tethered spinal cord and VACTERL association. **J Neurosurg 106 (3 Suppl):**201–204, 2007
14. Lew SM, Kothbauer KF: Tethered cord syndrome: an updated review. **Pediatr Neurosurg 43:**236–248, 2007
15. Long FR, Hunter JV, Mahboubi S, Kalmus A, Templeton JM Jr: Tethered cord and associated vertebral anomalies in children and infants with imperforate anus: evaluation with MR imaging and plain radiography. **Radiology 200:**377–382, 1996
16. Muthukumar N, Subramaniam B, Gnanaseelan T, Rathinam R, Thiruthavadoss A: Tethered cord syndrome in children with anorectal malformations. **J Neurosurg 92:**626–630, 2000
17. Pang D: Sacral agenesis and caudal spinal cord malformations. **Neurosurgery 32:**755–779, 1993
18. Quan L, Smith DW: The VATER association. Vertebral defects, anal atresia, T-E fistula with esophageal atresia, radial and renal dysplasia: a spectrum of associated defects. **J Pediatr 82:**104–107, 1973
19. Rendeli C, Ausili E, Tabacco F, Focarelli B, Massimi L, Caldarelli M, et al: Urodynamic evaluation in children with lipomeningocele: timing for neurosurgery, spinal cord tethering and followup. **J Urol 177:**2319–2324, 2007
20. Sasani M, Asghari B, Asghari Y, Afsharian R, Ozer AF: Correlation of cutaneous lesions with clinical radiological and urodynamic findings in the prognosis of underlying spinal dysraphism disorders. **Pediatr Neurosurg 44:**360–370, 2008
21. Spilde TL, Bhatia AM, Mehta S, Ostlie DJ, Hembree MJ, Preuett BL, et al: Defective sonic hedgehog signaling in esophageal atresia with tracheoesophageal fistula. **Surgery 134:**345–350, 2003
22. Tunell WP, Austin JC, Barnes PD, Reynolds A: Neuroradiologic evaluation of sacral abnormalities in imperforate anus complex. **J Pediatr Surg 22:**58–61, 1987
23. Warf BC, Scott RM, Barnes PD, Hendren WH III: Tethered spinal cord in patients with anorectal and urogenital malformations. **Pediatr Neurosurg 19:**25–30, 1993

Manuscript submitted September 21, 2009.
Accepted May 17, 2010.

Address correspondence to: Brent O'Neill, M.D., Division of Pediatric Neurosurgery, Seattle Children's Hospital, W7729, 4800 Sand Point Way NE, Seattle, Washington 98105-0371. email: boneill35@gmail.com.