

SIRENOMELIA WITHOUT VITELLINE ARTERY STEAL

F. Jaiyesimi, FRCP; T. Gomathinayagam, DMRD;
A. Dixit, MD; M. Amer, MD

Sirenomelia sequence is a rare malformation, the reported incidence being 1.5-4.2/100,000 births.¹ It is characterized by the presence of a single lower limb (simpus), which may have two feet (simpus dipus), one foot (simpus monopus), or no recognizable foot (simpus apus). The lower limb may be oriented anteriorly² or posteriorly.³

Current interests in the malformation center on its relationship to VACTERL (vertebral, anal, cardiovascular, tracheal, esophageal, renal and limb) association and its pathogenesis, particularly the reported role of a "vitelline artery steal,"⁴ vis-a-vis a primary defect in the formation of the caudal mesoderm and related structures.^{5,6} We report here a case which is remarkable in two aspects: 1) its very close similarity to VACTERL and more importantly, 2) the absence of a demonstrable arterial steal.

Case Report

The infant was born after 35 weeks of unsupervised pregnancy to a healthy 26-year-old gravida 7, para 6 mother. Delivery was by assisted breech. Apgar scores were 4 at one and 8 at five minutes, and both the birthweight (1740 g) and length (43 cm) reflected intrauterine growth retardation. The parents, who are not consanguineous, have five healthy children, and knew of no family history of malformations. Immediate postnatal examination revealed a severely malformed baby. There were features of Potter sequence, including retrognathia, hypertelorism, medial epicanthic folds, and rudimentary ears with no auditory meatus. Copious secretions poured out persistently from his mouth and nostrils, raising a suspicion of esophageal atresia. Cardiac evaluation was normal, but the umbilical cord contained only one artery. The anus and external genitalia were absent; only a 3x8 mm skin tag marked the position of the genitalia. Neither the urinary bladder nor the kidneys were palpable. This, in the setting of absent urethral opening, raised a suspicion of renal agenesis.

There was a single lower limb, but with two feet fused posteriorly. It was anteriorly oriented and held at fixed flexion relative to the trunk (Figure 1). Radiographs revealed that it contained the complete pairs of lower limb bones. Both hips were dislocated, and the sacrum pointed posteriorly.

Other malformations ascertained after further investigations included esophageal atresia with tracheo-esophageal fistula and duodenal atresia. Abdominal ultrasonography failed to demonstrate any internal genitalia, bladder or kidneys. The diagnosis of bilateral renal agenesis was further confirmed by the failure to demonstrate any dye excretion after intravenous urography. Echocardiography was normal, as was cranial ultrasonography.

Aortography, performed through an umbilical artery catheter, revealed tapering of the aorta along its course. It measured 9 mm at the level of T₄, 7 mm just above the diaphragm, and 5 mm at its bifurcation which, however, occurred normally at the level of L₄. The celiac artery appeared small and was poorly opacified. The renal and inferior mesenteric arteries were absent, while the other branches of the abdominal aorta appeared attenuated

TABLE 1. Main defects in caudal regression syndrome (CRS), VACTERL association and sirenomelia sequence.

Type or location of defect	Relative frequency (%)			Present patient
	CRS (N 153) ¹⁰	VACTERL (N 120) ¹⁰	Sirenomelia (N 134) [*]	
Vertebrae/sacrum/pelvis	100	100	100	+
Lower limb	73	30	100	+
Anorectal	0	88	97	+
Renal	26	85	93	+
Genital	3	55	85	+
Lower urinary tract	0	48	57	+
Single umbilical artery	0	10	79	+
Cardiac	0	24	26	-
Radial limb	0	29	21	-
Esophageal atresia ±TOF	0	28	5	+
Other GI defects	0	21	44	+
Respiratory tract (excluding TOF)	0	11	24	-
CNS	69	16	8	-

^{*}Based on data from Duncan et al. (54 patients)¹⁰ and Stocker and Heifetz (80 patients);¹ TOF=tracheo-esophageal fistula.

From the Departments of Pediatrics (Drs. Jaiyesimi, Dixit and Amer), and Radiology (Dr. Gomathinayagam), Buraimi Hospital, Buraimi, Sultanate of Oman.

Address reprint requests and correspondence to Prof. Jaiyesimi: P.O. Box 377, Code 512, Buraimi, Sultanate of Oman.

Accepted for publication 22 August 1998. Received 25 February 1998.

(Figure 2). The single umbilical artery, which was small as well, branched off normally from the right iliac artery at the level of L₅.

The baby succumbed on day 5. Cultural constraints precluded an autopsy.

Discussion

Duhamel coined the term “caudal regression syndrome” in 1961 to describe the association of sirenomelia with anorectal, genitourinary, and vertebral anomalies.⁷ Later, a distinction was made between sirenomelia sequence and caudal regression syndrome in the belief that the former had a specific pathogenetic factor, namely arterial steal, whereas the latter was probably a heterogeneous group with diabetic embryopathy as the single most frequently suspected etiological factor.⁸

In 1973, Quan and Smith⁹ proposed the acronym VATER to denote the non-random association of vertebral defects, tracheo-esophageal fistula with esophageal atresia, renal and radial limb defects. It was suggested that categorization as VATER required the presence of at least three of these defects. The acronym was later expanded to VACTERL in order to reflect the importance of associated cardiac and non-radial limb defects.

Lately, some authors have drawn attention to the overlap in the phenotypic manifestations of sirenomelia sequence and VACTERL.¹⁰⁻¹² Some idea about the extent of the overlap can be gleaned from Table 1, which we compiled by rearranging data from two major publications on these malformations.^{1,10} In the series by Stocker and Heifetz,¹ all 80 sirenomelics had at least three other VACTERL anomalies in addition to the limb defect. Similarly, 48 of the 50 sirenomelics analyzed by Duncan et al.¹⁰ had at least three of the six VACTERL ascertainment anomalies. Our patient had four VACTERL anomalies, excluding the simpus. It seems, therefore, that in most cases, the difference between sirenomelia sequence and VACTERL lies mainly in the severity of the component defects, with the single lower limb in sirenomelia being an epitome of other severe malformations, especially in the gastrointestinal and genito-urinary systems.

The etiology of sirenomelia sequence is uncertain, as no specific teratogens have been associated with the malformation in humans. However, an association with twinning is suspected. Its incidence is 100-150 times higher in monozygotic compared with dizygotic twins or singletons, and close to 20% of the reported cases were in products of twin pregnancies.^{1,11,13}

In view of the strong association between caudal regression syndrome and maternal diabetes mellitus,^{8,14,15} reports of sirenomelia in infants of diabetic mothers have aroused suspicion of a causal relation between the two diseases.¹⁵ However, a critical review of the literature shows that only 0.5%-3.7% of cases of sirenomelia

occurred in offspring of diabetic mothers,^{1,11,15} meaning that the association between maternal diabetes and sirenomelia is, at best, weak.

An inherited form of caudal dysgenesis has been recognized,¹⁶ and a few cases have also been attributed to aneuploidies, including trisomies 13 and 18, and 6q and 13q deletions.⁵ To date, however, there is no evidence of a genetic basis for sirenomelia sequence.

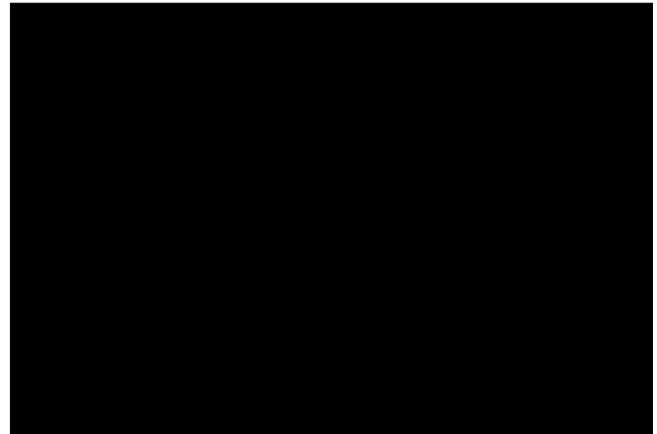


FIGURE 1. Composite illustration of the lower extremity in infant with sirenomelia. Left panel shows the fused lower limb with two feet (sympus dipus), but a radiograph of the limb (right panel) revealed that it contained the complete set of lower limb bones.

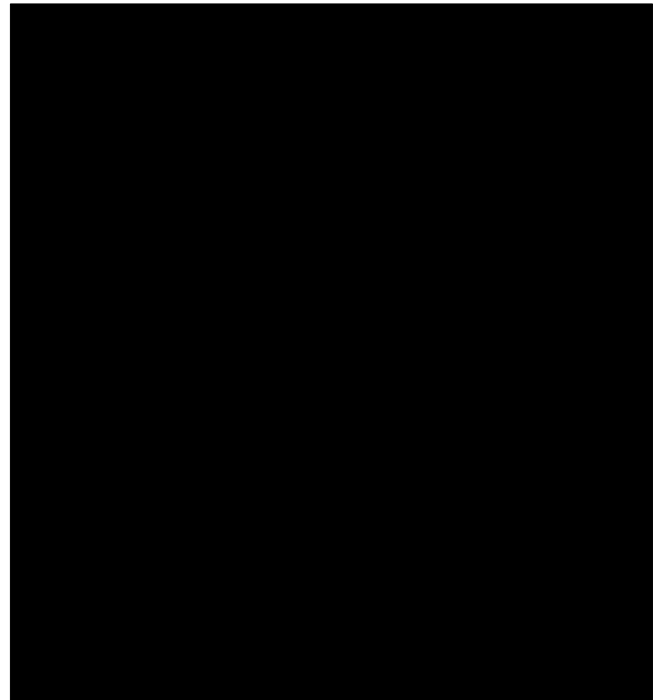


FIGURE 2. Transumbilical aortogram: the abdominal aorta tapers distally but remains the dominant artery. The inferior mesenteric and renal arteries are absent while the other branches of the abdominal aorta are attenuated and poorly opacified. The single umbilical artery (catheterized) arises from the right iliac artery at the level of L₅; it, too, is attenuated.

Like its etiology, the pathogenesis of sirenomelia sequence is also uncertain, and speculations on this theme are almost as varied as the clinical spectrum of the disease. In 1987, Stocker and Heifetz¹ summarized the theories proposed thus far. The most plausible among them were: 1) a defect in the primitive streak with subsequent malformation of the caudal region; 2) neural tube distension in the caudal region with lateral rotation of the mesoderm resulting in fusion of the hind limb buds; and 3) a defect of the midline structures, including cloacal and urogenital sinus derivatives, which allows approximation and fusion of the hind limb buds.

At about the same period, Stevenson et al.⁴ proposed the "vitelline artery steal" theory. They reported that in each of 11 sirenomelia specimens which they had studied, a large artery, presumed to be a derivative of the vitelline artery, arose from the aorta high in the abdominal cavity, beyond which point the aorta and its branches were hypoplastic. They stressed that "the major abdominal artery is, without exception, a derivative of the vitelline artery complex," and inferred that sirenomelia resulted from a "vitelline artery steal," which diverted blood and nutrients away from the caudal portion of the embryo to the placenta. That inference met with wide, but not unanimous, acceptance.^{2,3,5,8,17}

Earlier, Heifetz,¹⁸ reporting on a group of 25 sirenomelics in whom the umbilical cord was examined, stated that each had a single umbilical artery, which arose directly from the aorta just distal to the celiac axis. He suggested that the high origin of the single umbilical artery was unique to sirenomelia.

A different arterial pattern was noted in our patient. Although the aorta tapered along its course, it remained the major artery throughout. All its branches, including those derived from the vitelline artery (namely, celiac and mesenteric arteries), showed severe degrees of attenuation. In addition, the single umbilical artery arose normally from the iliac artery and, unlike those in the specimens studied by Stevenson et al.,⁴ it was not a large vessel. Clearly, that pattern is not consistent with a vitelline artery steal. On the contrary, the extremely small caliber of the celiac and mesenteric arteries suggests that the vitelline artery complex itself was hypoplastic.

Experimental studies have also been conducted with a view to ascertaining the pathogenesis of sirenomelia and related malformations. Recently, Alles and Sulik⁵ produced caudal dysgenesis in mouse embryos by exposing them to etretinate (a synthetic vitamin A analogue and potent teratogen) on the eighth day of gestation. The defect seemed to have resulted from excessive cell death in the primitive streak and hindgut endoderm. Similarly, Wei and Sulik⁶ produced sirenomelia, secondary to cell death in the caudal mesoderm, in chick embryos exposed to ochratoxin A (a fungal toxin) during organogenesis.

These laboratory findings, the absence of a demonstrable arterial steal in our patient, and the

occurrence in many other patients of defects proximal to the territory of the abdominal aorta,^{1,11,19} all suggest that factors other than vitelline artery steal can produce sirenomelia in humans. Excessive primary cell death in the caudal mesoderm and hindgut endoderm^{5,6} seems to be one such factor. Axial mesodermal dysplasia and midline developmental field defects have also been suggested as plausible mechanisms, especially in patients with cephalic and caudal defects.¹⁹

Acknowledgements

The authors gratefully acknowledge the assistance rendered by Drs. S.A. Adebonojo, Wright State University, Dayton, Ohio, and F.O. Akinbami, Sultan Qaboos University Hospital, Muscat, Oman. Mrs. Maria Teresita Apaoan and Mr. Nolan M. D'sa kindly typed the manuscript.

References

1. Stocker JT, Heifetz SA. Sirenomelia: a morphological study of 33 cases and review of the literature. *Perspect Pediatr Pathol* 1987;10:7-50.
2. Murphy JJ, Fraser GC, Blair GK. Sirenomelia: case of the surviving mermaid. *J Ped Surg* 1992;27:1265-8.
3. Egan JFX, Petrikovsky BM, Vintzileos AM, Rodis JF, Campbell WM. Combined pentalogy of Cantrell and sirenomelia: a case report with speculation about a common etiology. *Am J Perinatol* 1993;10:327-9.
4. Stevenson RE, Jones KL, Phelan MC, Jones MC, Barr M, Clericuzio C, et al. Vascular steal: the pathogenic mechanism producing sirenomelia and associated defects of the viscera and soft tissues. *Pediatrics* 1986;78:451-7.
5. Alles AJ, Sulik KK. A review of caudal dysgenesis and its pathogenesis as illustrated in an animal model. *Birth Defects* 1993;29:83-102.
6. Wei X, Sulik KK. Pathogenesis of caudal dysgenesis/sirenomelia induced by ochratoxin A in chick embryos. *Teratology* 1996;53:378-91.
7. Duhamel B. From the mermaid to anal imperforation: the syndrome of caudal regression. *Arch Dis Child* 1961;36:152-5.
8. Jones KL. Smith's recognizable patterns of human malformation. Philadelphia: W.B. Saunders Company, 1988:574-5.
9. 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* 1973;82:104-7.
10. Duncan PA, Shapiro LR, Klein RM. Sacrococcygeal dysgenesis association. *Am J Med Genet* 1991;41:153-61.
11. Duncan PA, Shapiro LR. Interrelationships of the hemifacial microsomia: VATER, VATER, and sirenomelia phenotypes. *Am J Med Genet* 1993;47:75-84.
12. Schuler L, Salzano FM. Patterns in multimaligned babies and the question of the relationship between sirenomelia and VACTERL. *Am J Med Genet* 1994;49:29-35.
13. Di Lorenzo M, Brandt ML, Veilleux A. Sirenomelia in an identical twin: a case report. *J Pediatr Surg* 1991;11:1334-6.
14. Fraser R. Diabetes in pregnancy. *Arch Dis Child* 1994;71:F224-F230.
15. Lynch SA, Wright C. Sirenomelia, limb reduction defects, cardiovascular malformation, renal agenesis in an infant born to a diabetic mother. *Clin Dysmorphol* 1997;6:75-80.
16. Lynch SA, Bond PM, Copp AJ, Kirwan WO, Nour S, Balling R, et al. A gene for autosomal dominant sacral agenesis maps to the holoprosencephaly region. *Nat Genet* 1995;11:93-5.
17. Tang TT, Oechler HW, Hinke DH, Segura AD, Franciosi RA. Limb body-wall complex in association with sirenomelia sequence. *Am J Med Genet* 1991;41:21-5.
18. Heifetz SA. Single umbilical artery. A statistical analysis of 237 autopsy cases and review of the literature. *Perspect Ped Pathol* 1984;8:345-78.
19. Rodriguez JI, Palacios J. Craniorachischisis totalis and sirenomelia. *Am J Med Genet* 1992;43:732-6.