Review Article
Sirenomelia: A Multi-systemic Polytopic Field Defect with Ongoing Controversies

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The most impressive phenotypic appearance of sirenomelia is the presence of a 180°-rotated, axially positioned, single lower limb. Associated gastrointestinal and genitourinary anomalies are almost always present. This rare anomaly is still the subject of ongoing controversies concerning its nosology, pathogenesis, and possible genetic etiology. Sirenomelia can be part of a syndromic continuum, overlapping with other complex conditions including caudal dysgenesis and VATER/VACTERL/VACTERL-H associations, which could all be part of a heterogeneous spectrum, and originate from an early defect in blastogenesis. It is imaginable that different "primary field defects," whether or not genetically based, induce a spectrum of caudal malformations. In the current study, we review the contemporary hypotheses and conceptual approaches regarding the etiology and pathogenesis of sirenomelia, especially in the context of concomitant conditions. To expand on the latter, we included the external and internal dysmorphology of one third trimester sirenomelic fetus from our anatomical museum collection, in which multiple concomitant but discordant anomalies were observed compared with classic sirenomelia, and was diagnosed as VACTERL-H association with sirenomelia.

Introduction

The most obvious phenotypic characteristic in sirenomelia (also called: symmelia or mermaid syndrome) is the single axially positioned lower limb. However, sirenomelia can be seen as a (lethal) multi-system condition based on a polytopic field defect with a wide phenotypical variability and frequently observed co-occurring with musculoskeletal, central nervous system, cardiopulmonary and other visceral anomalies, in addition to the almost always present gastrointestinal and genitourinary anomalies (reviewed by Gabriele and Gianpaolo, 2013). Sirenomelia is still the subject of debate, due to its ongoing controversies regarding its etiopathogenesis. Sirenomelia shows a heterogeneous phenotypic variability and overlap with caudal regression syndrome/sacro-coccygeal dysgenesis (Duhamel, 1961; Stocker and Heifetz, 1987; Adra et al., 1994), small pelvic outlet syndrome (Currarino and Weinberg, 1991), VATER/VACTERL (Young et al., 1986; Schüler and Salzano, 1994; Jain et al., 2002; Moosa et al., 2012), and VACTERL-H associations (Onyeije et al., 1998). There have been several attempts to classify these receptacles of caudal malformations, unfortunately without satisfying results. Clearly, diagnostic overlap exists between these conditions and the interpretation of their etiopathogenetic origin.

The purpose of this study is to give an overview of multiple facets of this dysmorphological puzzle and review what is known about the co-occurrence of sirenomelia and other birth defects, in particular those assigned to the VACTERL(-H) spectrum. The existing literature on these conditions is supplemented by one additional case of sirenomelia with a concomitant VACTERL-H association.

Sirenomelia

Sirenomelia is a rare, polytopic and multi-systemic anomaly named in analogy of the single axial positioned lower limb present in the mythical creatures "sirens" or "mermaids" (Fig. 1). These hybrid creatures were depicted in Greek mythology as half woman/half fish and portrayed as enchanting singing creatures who lured sailors to death (Romano et al., 2005). Although the mythical creature mermaid is more frequently depicted as a woman, the counterpart is the merman or Triton type sirenomelia, which is often depicted with a trident and a twisted conch shell to calm or raise the waves (Fig. 2). That the mermaid

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FIGURE 1. *The little mermaid in bronze by Edvard Erikson at the Langelinie promenade in Copenhagen, Denmark. From 1913, this statue is a Copenhagen icon and a major tourist attraction.*

is depicted more often than the merman is probably due to the more attractive nature of the female's hair, eyes, and bosom, thereby increasing its esthetic sensual attributes as the external genitalia were absent (Orioli et al., 2011). Sirenomelia intrigued mankind since the earliest times, as can be seen by a 2000-year-old terracotta pottery (Fig. 3) of the pre-Colombian Tumaco-Tolita culture, which clearly represented a case of sirenomelia (Pachajoa and Rodriguez, 2011). In the mid-16th century, the first objective descriptions concerning sirenomelia appeared and were ascribed to Rocheus in 1542 and Palfyn in 1553 (Kampmeier, 1927). In the early 18th century, sirenomelia was called monopodia or sympodia (Lhuaire et al., 2013). In the mid-19th century, Saint-Hilaire (1836) and Forster (1861) described cases of sirenomelia and named the three externally discernible variants of sirenomelia: (1) symèles or sympus dipus (presence of two feet), (2) uro-mèles or sympus monopus (presence of one foot) or (3) syrénomèle or sympus apus (no discernible foot). These essentially abandoned classifications focused on the degree of lower limb presence, denoted by the presence of the feet. It can be stated that, in general, the degree of absent foot structures correlates with the severity of the anomaly.

The currently used classification of sirenomelia is according to Stocker and Heifetz (1987), who classified sirenomelia into seven types based on the number of

FIGURE 2. *Copperplate from the book: A General Treatise of the Dominion of the Sea: and a Compleat Body of the Sea-laws by T. Page, W. and F. Mount, 1724. Neptune wielding British flags at sea. In the lower right corner, a triton or merman is depicted which is blowing on his conch to calm or raise the waves.*

FIGURE 3. *Terracotta pottery from the pre-Colombian Tumaco-Tolita culture, which clearly represented a case of sirenomelia.*

skeletal elements present in the lower limb. However, the classifications can be considered nothing more than discrete groups of a sirenomelic spectrum (Orioli et al., 2011). Additionally, reports exist in which sirenomelic fetuses do not fit in the Stocker and Heifetz classification (Lhuaire et al., 2013). This was due to the presence of dysmorphological ossified structures in the lower limb that did not correlate with one of the seven types. Moreover, efforts are reported for a proposed extended classification of sirenomelia that was based on measurements on the iliac–sacral distance, indicating the need for reviewing and elucidating the classification of sirenomelia (Kjaer et al., 2003). An overview of the existing classifications of sirenomelia is given in Table 1.

Familial Recurrence and Occurrence of Sirenomelia

True recurrence of sirenomelia was reported in only one family with two of five affected by sirenomelia (Rudd and Klimek, 1990). These authors proposed evidence for a major dominant gene (with reduced penetrance) in familial caudal malformations. However, a comprehensive study from Orioli et al. (2011), concerning 249 cases of sirenomelia, reported no familial recurrence of sirenomelia. Familial occurrence of sirenomelia in one and urogenital and/or anorectal anomalies in other individuals have been described repeatedly. Selig et al. (1993) reported a family where three siblings and a maternal aunt had renal

TABLE 1. *Overview of the Classifications of Sirenomelia*

Saint-Hilaire (1837) and Forster (1865) classification based on the presence of the feet	
Type I	Symèles or sympus dipus (presence of two feet)
Type II	Uromèles or sympus monopus (presence of one foot)
Type III	Syrénomèle or sympus apus (no discernible foot)
Stocker and Heifetz (1987) classification based on presence of ossified structures	
Type I	Presence of two separated femurs, two tibiae, and two fibulae
Type II	Presence of two separated femurs, two tibiae, and a medially fused fibula
Type III	Presence of two separated femurs, two tibiae and no fibula
Type IV	Presence of a partially fused femur, two tibiae, and a medially fused fibula
Type V	Presence of a partially fused femur, two tibiae, and no fibula
Type VI	Presence of a complete fused femur and a single fused tibia
Type VII	Presence of a complete fused femur
Kjaer et al. (2003) classification based on the ISD	
Normal ISD	Separate ilia and femora
Mildly increased ISD	Fused ilia or femora
Greatly increased ISD	Single iliac and femur bones

Note that the first two classifications are applied and propagated most widely and are often intertwined when describing sirenomelic fetuses. The 2003 classification is included for its completeness but is actually very little used.

ISD, iliac-sacral distance

anomalies consistent with renal dysplasia (renal agenesis, cystic dysplastic kidneys, and urethral valves). A fourth sibling had sirenomelia. Both parents had normal renal ultrasound examinations. Other reports concern monozygotic twins in which one of the twins was affected by sirenomelia and the other by imperforated anus (Akbiyik et al., 2000). Gerard et al. (2012) described a mother who had undergone surgery for an imperforate anus and whose first pregnancy was terminated because of bilateral renal agenesis in the fetus. Her second pregnancy was complicated by sirenomelia. In another family, a firstborn child had imperforate anus, absence of S3–S5 and coccyx, abnormal pelvic floor, and bifid bladder, whereas the second child was affected by sirenomelia. No diabetes was present during the pregnancies in either of these two families.

Assimakopoulos et al. (2004) described two cases of diabetic, dizygotic twin pregnancies, each with one normal and one affected fetus. In the first twin pregnancy the affected fetus had caudal regression syndrome, and the other was normal. In the second twin pregnancy the affected fetus suffered from sirenomelia and the other twin showed no abnormalities. Additionally, Gabriele and Gianpaolo (2013) reviewed the familial occurrence of sirenomelia and found five singleton related cases and nine twin related cases of caudal malformations. A report by Rigon et al. (2013) described sirenomelia followed by a caudal mesodermal defect in a sibling. These cases of familial occurrence of sirenomelia and other caudal dysgenesis-related conditions are suggestive of shared intrinsic (i.e., genetic) and/or extrinsic (i.e., teratogenic) etiopathogenetic elements.

Maternal Diabetes and Twinning in Sirenomelia

The only maternal disease that has been described to be associated with sirenomelia is diabetes mellitus. It is believed that one in five sirenomelic children are born to a diabetic mother (Al-Haggar et al., 2010). However, Oriolli et al. (2011) reported that it was impossible to confirm this relative high prevalence. Multiple reports are present that describe mothers with diabetes mellitus who gave birth to sirenomelic children. Both Gürakan et al. (1996) and Lynch and Wright (1997) reported sirenomelia in an infant born to a diabetic mother and stated that the association of sirenomelia and maternal diabetes is somewhat controversial and has not been firmly established. Moreover, Castori et al. (2010) reported a diabetic mother who had three pregnancies, one sirenomelic child, one miscarriage, while the third was terminated for fetal malformations, diagnosed postmortem as VACTERL association, indicating a possible causal relationship. Additionally, reports exist of caudal dysgenesis without maternal diabetes mellitus (Yeniel et al., 2011). Gabriele and Gianpaolo

(2013) reported that sacro-coccygeal dysgenesis (caudal regression syndrome) is strongly associated with diabetes mellitus (21–28%) while imperforate anus, a constant finding in sirenomelia, is a less common anomaly in caudal dysgenesis, even in its most severe form.

Multiple reports exist that correlate diabetes mellitus and caudal malformations and vice versa. Although the co-occurrence of maternal diabetes mellitus in sirenomelia and in other caudal malformations has not been firmly established, it seems possible that at least cases of sirenomelia have an etiopathogenesis linked to maternal diabetes.

It is generally accepted that sirenomelia occurs more frequently in monozygotic twin pregnancies (Murphy et al., 1992). Escobar (1990) reported that the frequency of sirenomelia is 8 to 10% higher in twinning, and approximately 100 to 150 times higher in monozygotic twins, with respect to dizygotic twins or singletons. Schinzel et al. (1979) reported that 7% of sirenomelic children were part of monozygotic twins and Thottungal et al. (2010) reported an incidence of 11% of sirenomelia that were part of monozygotic twins. The possible correlation between sirenomelia and twinning has yet to be elucidated.

Prevalence, Prenatal Diagnosis, and Prognosis of Sirenomelia

The birth prevalence of sirenomelia is estimated by Orioli et al. (2011) to be 0.98 per 100,000 births. Due to the absence of external genitalia in sirenomelia and the often missing information on gonadal or chromosomal sex, data concerning the male–female ratio are very limited. Interestingly, Källén et al. (1992) described an increased risk for sirenomelia under the maternal age of 20 and above the age of 40; however, these finding were not statistically significant. A large epidemiologic study by Orioli et al. (2011) noted an increased risk for sirenomelia with maternal ages less than 20. Strangely, the co-occurrence of maternal diabetes or twinning in sirenomelia are usually associated with higher maternal ages.

Sirenomelia can be diagnosed during prenatal screening by, for example, transvaginal or abdominal ultrasonography (Sepulveda et al., 1994; Van Zalen-Sprock et al., 1995; Liu et al., 2015) and fetal MRI (Van Keirsbilck et al., 2006). Often this three-dimensional (3D) prenatal ultrasonographical screening is hindered by the presence of severe oligohydramnios (Patel and Suchet, 2004). However, bladder and renal agenesis, lumbosacral defects, and lower limb abnormalities are almost always present in sirenomelia and can be detected during screening. The earliest detection of sirenomelia was at 9 weeks (reviewed by Gabriele and Gianpaolo, 2013). Thottungal et al. (2010) reported five of nine sirenomelic fetuses with normal amniotic fluid volumes, due to the timing of prenatal

screening and the dominance of maternal contribution to the amniotic fluid volume; a narrow window is present between gestational weeks 8 and 16 when the limb structures can be visualized with ultrasound and the amniotic fluid volume is still depending on maternal production (Orioli et al., 2011).

The overall prognosis of sirenomelia in terms of survival is very poor and mainly depends on the severity of the urogenital abnormalities and the resulting oligohydramnios and lung hypoplasia (Lutz et al., 2004). Only a few exceptional cases of surviving newborns have been reported (Guidera et al., 1991; Murphy et al., 1992; McCoy et al., 1994; Goodman et al., 1996; Stanton et al., 2003; Messineo et al., 2006).

Teratogenically Induced Sirenomelia

Teratogenic drug induced sirenomelia in humans has only been scarcely reported. Sarpong and Headings (1992) reported two cases of cocaine abuse during the first trimester of pregnancy, which supposedly led to vasoconstriction and sirenomelia. A study by Holmes (2002) found no plausible teratogens that were associated with sirenomelia. However, Taghavi et al. (2009) reported a case of sirenomelia after heavy use of snuff-tobacco. Orioli et al. (2011) studied a large cohort of 249 sirenomelic fetuses and found only one case of possible teratogenic induced sirenomelia after misoprostol (an anti-peptic ulcer drug) use. Additionally, fever ($>38°C$) in the first trimester of pregnancy was reported in six cases of sirenomelia. Dosedla et al. (2012) described sirenomelia after exposure of the antibiotic trimethoprim and Tica et al. (2013) described a sirenomelic stillborn in a pregnant epileptic patient who used phenobarbital and carbamazepine during her pregnancy. A report by Cozzolino et al. (2016) concluded that early administration of methylergonovine maleate, a drug used to prevent and control postpartum haemorrhage, would cause sirenomelia.

In addition to human studies, animal studies showed that sirenomelia could be induced by administration of a combination of cadmium and lead in the golden hamster (Hilbelink and Kaplan, 1986), ochratoxin A (a fungal toxin) in chickens (Wei et al., 1996), and retinoic acid in rats (Padmanabhan, 1998). Hence, multiple papers described teratogens causing sirenomelia. Nevertheless, teratogens are very discrete in their nature, and determination of true teratogenic mechanisms remains complicated. Many potential mechanisms, pathogenetic routes, and ultimate morphological outcomes are present, which makes it very difficult to elucidate certain teratogens that induce congenital anomalies (reviewed by Alexander and Tuan, 2010; Alexander et al., 2016). Although some studies apparently report a relationship between sirenomelia and certain drugs, these findings are statistically weak and can very well be coincidental findings.

Sirenomelia in Chromosomal and Monogenetic Conditions

Multiple studies exist that report chromosomal and monogenetic alterations in sirenomelia. A study by Orr et al. (1982) described craniofacial, caudal, and also visceral anomalies in sirenomelic mice, in which the *Srn* gene is considered to be responsible for causing sirenomelia. Abu-Abed et al. (2001) reported one occurrence of sirenomelia in *Cyp26A1*-null mutant mice. Noteworthy is that the superfamily of *Cyp* genes are cytochrome oxidases regulating the metabolism of ingested chemicals, and thus could be responsible for increased sensitivity to environmental toxins. *Cyp26A1* is the receptor of retinoic acid. Malformations of the lower vertebral column have been reported in pregnancies exposed to high doses of retinoic acid at different gestational ages, linking sirenomelia and retinoic acid intoxication (Kessel and Gruss, 1991).

Moreover, Zakin et al. (2005) found frequent occurrence of sirenomelia in *Tsg-/-; BMP7-/-* mice and frogs. This report also stated that *OTX2* expression, which is an anterior marker, was significantly increased in the forebrain of *Xenopus* embryos that were inactivated for *Tsg* and *BMP7* by antisense MO oligonucleotides. Susuki et al. (2012) reported a new mouse model with a *Isl1Cre;Bmp4(-flox/flox)* condition that was associated with sirenomelia. Garrido-Allepuz et al. (2012) reported that the removal of one or both functional alleles of the Sonic Hedgehog (*SHH*) gene leads to a sirenomelia phenotype in mice. Very few chromosomal conditions have been reported in human cases of sirenomelia. Kurosawa et al. (2012) found a de novo balanced 46,X,t(X;16)(p11.23;p12.3) translocation. Gabriele and Gianpaola (2013) described a triploidy mosaic sirenomelic fetus (69,XXX/46,XX) after karyotyping the chorionic villi. Evidently, more research is needed to correlate the reported genetic and chromosomal conditions with the etiology and pathogenesis of sirenomelia.

Sirenomelia and its Overlap with Caudal Dysgenesis

An often cited theory postulates that caudal dysgenesis and sirenomelia belong to the same heterogeneous spectrum. Caudal dysgenesis is hypothesized to arise from a primary deficiency of caudal mesoderm (Duhamel, 1961; Alles and Sulik, 1993). This theory is supported by many authors (e.g., Duesterhoeft et al., 2007; Charlier et al., 2008; Thottungal et al., 2010; Gerard et al., 2012; Seidahmed et al., 2014; Moosa et al., 2012; Das et al., 2013; Lhuaire et al., 2013; Kaygusuz et al., 2016). Dias and Walker (1992) suggested that a teratogenic event occurred during gastrulation that interfered with the formation of the notochord, resulting in abnormally developed caudal structures and concomitant neural tube defects.

A noteworthy article from Padmanabhan (1998), presented the entire spectrum from caudal dysgenesis to

sirenomelia in retinoic acid induced malformations in the rat, with the severity of caudal malformations depending on dose and timing of drug administration. However, multiple papers exist that separate the two entities, and assert that sirenomelia and caudal dysgenesis are unrelated and have their own etiopathogenetic origin. Duncan et al. (1991) showed that patient survival, twinning, and the high incidence of maternal diabetes were arguments to support its differentiation. Twickler et al. (1993) described sonographic differences and maternal specific characteristics to separate both entities. Perez-Aytes et al. (1997) separated both entities based on differences in angiography, and Bruce et al. (2009) described the characteristics of nine cases with caudal dysgenesis syndrome and six with sirenomelia, and concluded that both anomalies share similar features but are two different entities. This conclusion was based on comparison of the available clinical information, maternal follow-up, macroscopic and microscopic findings from autopsies, surgical pathology reports, radiographs, and differences in placenta morphology. At present, opinions remain divided as to whether the two conditions are etiopathogenically related, and if so, to what extent.

Overview of Etiopathogenetic Mechanisms

Due to lack of knowledge about the exact etiology and the clinical heterogeneity of sirenomelia regarding concomitant disorders, there are currently many hypotheses concerning its pathogenesis (reviewed by Valenzano et al., 1999; Garrido-Allepuz et al., 2011; Arvind Athavale, 2012; Gabriele and Gianpaolo, 2013; Kaygusuz et al., 2016). Below, we will describe the most cited ones and try to give an overview of the many existing hypotheses.

Bolk (1899) postulated that sirenomelia was the result of a defect in the formation of the caudal somites and that the extension of the defect would depend on the number of absent somites. In 1904, Ballantyne proposed that the absence of a tail bud led to the merging of the limb buds in sirenomelia. Russel et al. (1981) suggested the term "axial mesodermal dysplasia" to describe a disturbance during early embryogenesis that affects the mesodermal cell migration during primitive streak period. Subsequently, Opitz and Gilbert (1982) noted that the midline developmental field in early embryogenesis is a weakly buffered field, vulnerable to malformation. In 1987, Chandelbois and Brunet reported an anterioposterior elongation of the brain in a sirenomelic fetus with a concomitant overdeveloped nasal fossa, and hypothesized that the neural crest migration was accelerated and induced an overdevelopment of the rostral part and hypoplasia of the caudal parts.

In the same year, Stocker and Heifetz (1987) postulated that an "embryologic insult" to the caudal mesoderm, occurring between 28 and 32 days of gestation, was responsible for causing sirenomelia. In 1989, O'Rahilly and Müller, stated that sirenomelia occurred through a failure in lateralization that was secondary to a mesenchymal deficiency of the caudal development. Padmanabhan (1998) suggested that a mechanical defect resulting from lateral compression by amniotic folds caused sirenomelia. Ohta et al. (2007) stated that a defect in the formation of the primitive streak during late gastrulation could lead to caudal body malformations, including part of the urogenital/reproductive organs as well as the hind limbs. The primitive streak contributes to the ventral ectodermal ridge: a putative signaling center responsible for tail elongation by controlling cell proliferation in the underlying mesoderm (Gruneberg, 1956).

Obviously, most of the theories cited here are merely conceptual conjectures without any supporting evidence. The most propagated theory is the "vascular steal hypothesis", which is based on the typical presence of a single aberrant umbilical artery in most cases of sirenomelia. This vessel is interpreted as a persistent vitelline artery that originates superiorly from the abdominal aorta (Kampmeier, 1927; Stevenson et al., 1986). This aberrant vessel would divert the blood away from the caudal parts of the developing embryo, eventually resulting in underdevelopment or absence of caudal structures, as is the case in sirenomelia. In this perspective, the previously mentioned study by Wei et al. (1996) is relevant, which described that administration of ochratoxin A in chickens caused sirenomelia: this study underlines that the vascular steal hypotheses is unlikely to be the cause of sirenomelia; chickens lack placentas and the vitelline artery normally dominates the allantoic vascular supply.

Heifetz (1984) supported this theory when he observed a single umbilical artery in all of the 25 included sirenomelic fetuses. However, this vascular steal theory fails to explain the frequently associated anomalies, unrelated to the caudal area, that are observed in many sirenomelic fetuses (Källén and Winberg, 1974; Gariddo-Allepuz et al., 2011). Moreover, it seems that this single umbilical artery is not present in all cases and is not unique for sirenomelic fetuses. Multiple authors (Kohler, 1972; Jaiyesimi et al., 1998; Opitz et al., 2002; Thottungal et al., 2010) described the presence of two umbilical arteries in combination with sirenomelia, albeit of abnormal origin. Additionally, aberrant umbilical arteries have also been described in individuals with caudal dysgenesis (Hentschel et al., 2006; Duesterhoeft et al., 2007) and persistent vitelline arteries in otherwise normal fetuses (Gamzu et al., 2002). Perhaps the common finding of a single umbilical artery is a consequence of sirenomelia rather than its cause.

Another often cited hypothesis is the "defective blastogenesis hypothesis" which is correlated with the overall malformed caudal structures in sirenomelia and its relationship with defective development of the caudal somites

and tailbud (Stocker and Heifetz, 1987). According to this theory, sirenomelia is a primary defect of blastogenesis that occurs during the final stages of gastrulation at the tailbud stage (Opitz et al., 2002). The phenotypical variability depends on the intensity and duration of the blastogenetic event. The vascular steal hypothesis and the deficient blastogenesis hypothesis do not exclude each other, it is conceivable that a defect in early blastogenesis would concomitantly affect (targeted) organs by ischemia and deficiencies in nutrients by aberrant vessel development in later embryological development (Garrido-Allepuz et al., 2011; Lhuaire et al., 2013). Moreover, these pathophysiological hypotheses could be interrelated and constitute a similar etiopathogenetic continuum.

Presence of Neural Tube Defects and Holoprosencephaly

Surprisingly, approximately 10% of the sirenomelic fetuses show concomitant neural tube defects (Thottungal et al., 2010), including anencephaly (Schwaibold et al., 1986; Rodríguez et al., 1991), anencephaly with cervicothoracic meningocele (Pfeiffer and Becker, 1988), (myelo)meningocele (Gupta et al., 1992; McCoy et al., 1994; Chen et al., 1998), craniorachisischis totalis (Battaglia and Fraccaro, 1954; Rodríguez and Palacios, 1992; Halder et al., 2001), and spina bifida (Kulkarni et al., 1994; Chen et al., 1997). Browne et al. (2004) described the first case of sirenomelia with an angiomatous lumbosacral myelocystocele. It is known that the caudal eminence contributes to the formation of neural primordial, lower limb buds, perineum, hindgut, and blood vessels (Müller and O'Rahilly, 2004); an extensive disturbance of the axial mesoderm would cause a concomitant alteration of neural ectoderm and subsequently a neural tube defect.

Multiple authors reported co-occurrence of sirenomelia and holoprosencephaly (HPE) in the same individual (Young et al., 1986; Källén et al., 1992). As mentioned before, Garrido-Allepuz et al. (2012) reported that removal of one or both functional alleles of the Sonic Hedgehog (*SHH*) gene leads to sirenomelia in mice; *SHH* mutations are known to cause HPE (Roessler et al., 1996). Additionally, Shirani et al. (2006) reported sirenomelia in combination with agenesis of the corpus callosum in a human fetus, which is a key feature of HPE. This would suggest an additional developmental defect of the prechordal plate mesoderm in these sirenomelic fetuses resulting in HPE (Chen et al., 1997; Martínez-Frías et al., 1998). Moreover, sirenomelia and HPE are reported to occur in the same geographical region, indicating a possible common etiology in these specific cases (Castilla et al., 2008). Indeed, both sirenomelia and HPE are severe anomalies that involve a defect in the median plane that appear through a failure of lateralization (O'Rahilly and Müller, 1989). Opitz and Gilbert (1982) postulated that the midline is a weak buffered field during early embryogenesis and is prone to a midline field defect.

Associated "Non Classical" Anomalies in Sirenomelia

Many clinical case studies exist on the topic of sirenomelia. In the 167 articles identified in a PUBMED search *(sirenomelia[-Title/Abstract] AND hasabstract[text] AND "humans"[MeSH Terms])*, many case studies reported the same spectrum of anomalies that we consider to be part of the classical sirenomelia sequence, including a single midline lower limb, internal and external urogenital anomalies, large bowel (blind ending colon), pelvic, sacral and spinal defects, aberrant umbilical arteries, and Potter facies, due to oligohydramnios. It is beyond the scope of this review to include all these case studies. However, some papers are noteworthy because they report associated anomalies normally discordant in "classic" or "isolated" sirenomelia, they included a nephroblastoma (Kimura et al., 1975), neuroblastoma, and gallbladder agenesis (Drossou-Agakiou et al., 2004), double inferior vena cava (Goodlow et al., 1988), pentalogy of Cantrell (Egan et al., 1993), acardia (Zanforlin Filho et al., 2007), dextrocardia (Cavaliere et al., 2009), situs inversus totalis (Langer et al., 1996; Sivridis et al., 2002; Rougemont et al., 2008), limb-body wall complex (Tang et al., 1991; Martínez-Frías et al., 1992), and amniotic band disruptions sequence (Managoli et al., 2003).

A comprehensive review from Källén et al. (1992) reviewed 92 sirenomelic infants and found the following discordant anomalies: neural tube defects, hydrocephalus, cyclopia, cleft lip/palate, otocephaly, choanal atresia, esophageal atresia, tracheal agenesis/atresia, malrotation of gut, gall bladder agenesis, persistent vitelline duct, cardiac septal defects (ventricular septal defect [VSD], atrioventricular septal defect ASD), common arterial trunk, single ventricle, tricuspid atresia/single atrium, limb-body wall complex, diaphragmatic hernia, prune belly, double uterus-vagina, polydactyly, radial defects, transverse arm reduction, simian creases, thoracic vertebral anomalies, and absent lung lobe.

Another noteworthy study from Orioli et al. (2011) reported associated anomalies in 249 sirenomelic fetuses which included: pre-axial polydactyly, lobster claw hands, webbed upper limbs (pterygium), radial aplasia/hypoplasia, upper and postaxial limb reductions, joint contractures, hydrocephalus, microcephaly, spina bifida, esophageal atresia/fistula, oral clefts, microtia, eye defects (microphthalmia), ocular hypertelorism, HPE, abdominal wall defects (gastroschisis/omphalocele), diaphragm defects, anal and intestinal duplication, duodenal atresia, ectopia cordis, dextrocardia, tetralogy of Fallot, single ventricle, heart hypoplasia, persistent superior vena cava, bladder exstrophia, horseshoe kidney, hydronephrosis, spleen agenesis, and lung lobulation defects. López-Valdez et al. (2013) found hemifacial macrosomia and Bermejo et al. (2014) found a sirenomelia with associated truncus arteriosus. The

presence of many associated anomalies advocates that the etiopathogenesis of sirenomelia is complex, and perhaps originates from multiple developmental field defects, due to different genetic and/or environmental disturbances.

Sirenomelia and its Overlap with VATER/VACTERL(H) Associations

The many concomitant anomalies in sirenomelia mentioned previously include some that are part of the so called VA(C)TER/VACTERL association. This association is a statistically nonrandom constellation and acronym that includes at least three of the following core abnormalities: costo-vertebral segmentation defects (V), anal atresia/stenosis (A), cardiovascular defects (C), tracheo-esophageal fistula and/or esophageal atresia (TE), renal anomalies (R) and, in the VACTERL association, (radial) limb anomalies (L) (Khoury et al., 1983; Czeizel, 1984; Botto et al., 1997; Sözübir et al., 2000). Interestingly, the acronym is sometimes expanded to VACTERLS to include single umbilical artery. Moreover, the VACTERL association was extended by including hydrocephaly and designated as VACTERL-H association or Briard Evans syndrome (Briard et al., 1884; Evans et al., 1989). In contrast to the often sporadically occurring cases of VACTERL, this VACTERL-H appears to be a hereditary entity with both autosomal recessive and X-linked forms (Evans et al., 1989).

In addition to its sporadic presentation, VACTERL association has been reported as part of syndromic conditions, including trisomy 18, Townes-Brocks syndrome and, particularly, Fanconi anemia. The prevalence of VACTERL(H) phenotypes in Fanconi anemia patients ranges from 5% to as much as 44%, depending on the mutated gene (Alter et al., 2007; McCauley et al., 2011; Savage et al., 2016; Mikat et al., 2016). Multiple reports exist that describe VACTERL(-H) associations in combination with sirenomelia (Onyeije et al., 1998; Charlier et al., 2008; Castori et al., 2010; Moosa et al., 2012; Lhuaire et al., 2013) and several more in which the concomitant conditions were not recognized as being part of the VACTERL(H) association (see previously). Intriguingly, disturbances in the *Shh* signaling pathway in mice causes a VACTERL-like phenotope (Kim et al., 2001), in addition to its role in both sirenomelia and HPE (see previously). So far, gene mutations in infants with VACTERL-H associations and concomitant sirenomelia have not been reported.

External and Internal (Dys)Morphological Description of One Additional Sirenomelic Specimen from Our Museological Collection

Many anatomical museums around the world contain, maintain, and exhibit third trimester fetuses with severe congenital anomalies. These museological accumulations of
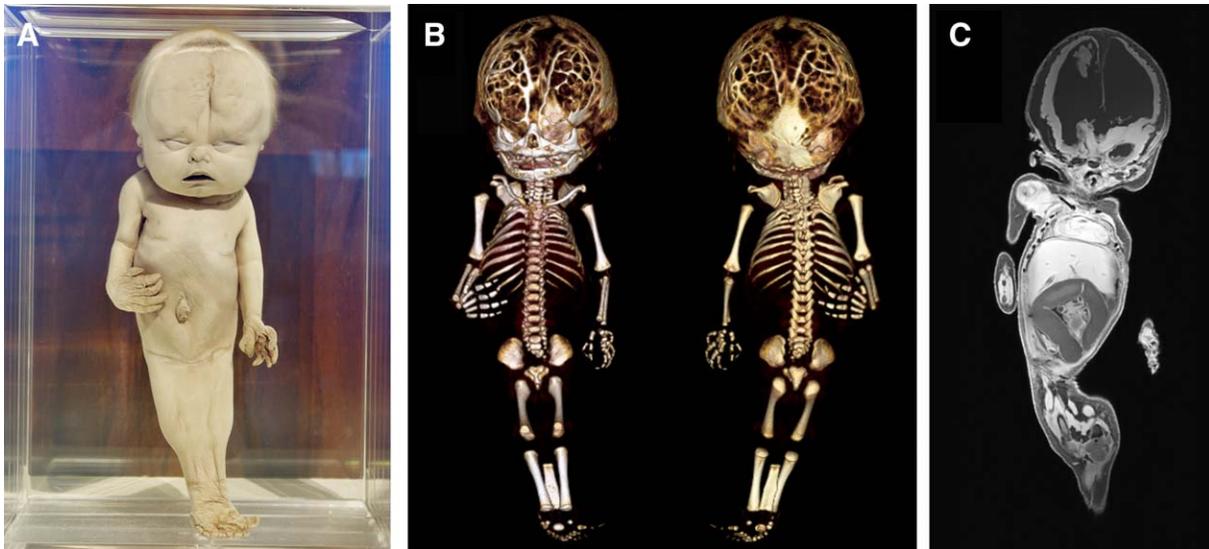

FIGURE 4. (**A**) *Photograph of the full term fetus.* (**B**) *Three-dimensional reconstructed skeletons based on the CT data showed an extensive hydrocephaly; multiple block-, hemi-, and butterfly vertebrae in the cervical and thoracic region; fused ribs; cervical ribs; and absence of the seventh cervical vertebra. The second and third sacral vertebrae were fused and the fourth and fifth sacral vertebrae were hypoplastic and dorsally oriented. The coccygeal vertebrae were completely absent. The left hand showed pre-axial polydactyly. The pelvic and lower limb region of the body showed the distinctive features of sirenomelia. Note: Left reconstruction depicts a frontal view, the right reconstruction depicts a dorsal view. The partially translucent appearance of the skull is a digital artifact that arises at a certain threshold value that is used during three-dimensional reconstruction of CT data. (**C**) T1-weighted coronal MRI image showed an extensive hydrocephalus with an absent septum pellucidum and absent corpus callosum. A malrotation of the intestines with a blind ending dilated and elongated sigmoid was seen. The internal and external urogenital characteristics were completely absent. Moreover, a double superior vena cava, a large VSD and a single right umbilical artery that inserted high in the abdominal aorta were detected.*

nature's capriciousness can be seen as irreplaceable treasure chests that provide a wealth of information for the study of rare, and mostly lethal, malformations beyond the scope of individual "clinical case studies" (Suarez and Tsutsui, 2004; Holmes et al., 2016). Additionally, these (predominantly) historical collections are exceptionally valuable, because most specimens were collected before the ubiquitous availability and usage of prenatal screening and, therefore, often presented well into the third trimester. Nowadays, these near full-term fetuses are a rare phenomenon in well-developed countries, where prenatal screening is an important element in monitoring the progress and development of the unborn child during pregnancy (Benson and Doubilet, 2014). Investigation of a museological specimen, like the one described here, can yield valuable contributions.

Our sirenomelic fetus was scanned with high-resolution radiological techniques (Boer et al., 2017) and comprehensively described, according to modern dysmorphological insights (Gorlin et al., 1990; Hall, 2006). A short external and internal dysmorphological description is summarized. This specimen concerns a full-term ambiguous sirenomelic fetus with a symmetric intrauterine growth restriction, a single axial positioned lower limb with a single foot and anteriorly faced sole, extensive hydrocephaly, pre-axial polydactyly and Potter's facies with hypertelorism, down slanting palpebral fissures, recessed nose, microretrognatism, and a low-set of ears. A presacral opening was seen that could be interpreted as an imperforated anus (Fig. 4A). Radiological data revealed several skeletal anomalies, in addition to the distinctive features of sirenomelia, and included rib and vertebrae anomalies and polydactyly (Fig. 4B). The MRI data showed, in addition to the distinctive urogenital anomalies in sirenomelia, an extensive hydrocephalus. Moreover, visceral anomalies included a malrotation of the small intestine, a double superior vena cava, a large VSD and a single umbilical artery (Fig. 4C–E). We diagnosed this case as VACTERL-H with concomitant sirenomelia type 2.

Conclusions

Sirenomelia and the many observed caudal malformations, including VACTERL-(H) associations, in all its forms and shapes, with all its co-occurring anomalies, show a complex heterogeneous spectrum, that is not covered by any of the current pathogenetic theories. From a more meta-theoretic level, Opitz et al. (2002) postulated that these anomalies arise as a result of a primary defect (i.e., gene mutation, environmental determinant, or interaction of both), affecting multiple midline primordia in early blastogenesis onto final gastrulation. This primary defect results in so-called "polytopic field defects." Opitz (1993) defined developmental fields as morphogenetically reactive units present during early development that lead to a final

structure that can be malformed in a similar manner, albeit by different causes. Therefore, clinically, a field is recognized when an identical malformation of a complex anatomical structure is proven to be caused by different factors. Thus, if one demonstrates heterogeneity in a pattern of anomaly, then that pattern is a developmental field defect.

The observed phenotypic variability may depend on the intensity, time of initiation, and duration of the underlying event (Kulkarni et al, 2004; Garrido-Allepuz et al., 2011). Additionally, the final phenotype will be influenced on the disease modifying genes, which can be divided into those uniquely affected by the primary mutation and those whose actions reflect generic responses to stress evoked by the principal mutation, then called intermediate phenotypes (Orioli et al., 2011).

It can be hypothesized that multiple "early developmental defects," such as vascular defects (vascular steal), defective blastogenesis, and the many other stated hypotheses, could all cause some sort of caudal malformation. Timing, intensity, duration, and secondary induced effects of these pathogenetic events could cause a heterogeneous spectrum of different entities that include sirenomelia and VACTERL(H) phenotypes.

It remains very difficult to point to a specific cause to the origin of many caudal malformations. It is known that retinoic acid can induce an entire spectrum between sirenomelia and caudal dysgenesis (Padmanabhan, 1998); however, maternal diabetes seems to be a predisposition for the latter, and reports exist that correlate maternal diabetes with sirenomelia (e.g., Orioli et al., 2011). It may be imagined that VACTERL with retinoic acid induced teratogenicity and presence of maternal diabetes can perhaps give some insight into a causal relationship. Another promising mechanism worthy of exploration for its potential pathogenetic role is the *Shh* signaling pathway, which, at least in mouse models, seems to be involved in both sirenomelia and caudal dysgenesis, as well as in VACTERL. Because each complex developing embryological structure involves concatenated networks, integrated biological and molecular expertise is necessary to unravel these rare polytopic field defects in blastogenesis and their associated genetic mutations. It is, therefore, important to adequately perform clinical diagnostics and (prenatal) imaging to clarify these still complex patterns of (caudal) malformations, and to get a clear overview of the complete morphological spectrum of associated conditions.

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