Tomasz MACHAŁOWSKI[a], Ahmad DABA'N[b], Najda TICIC[b], dr n. med. Michał Marian SKOCZYLAS[c], dr n. med. Marcin SAWICKI[d], prof. dr hab. n. med. Anna WALECKA[d]

Pomeranian Medical University in Szczecin:
Students' Scientific Circle in Department of Diagnostic Imaging and Interventional Radiology:
[a] Polish program, [b] English program
[c] Department of Diagnostic Imaging and Interventional Radiology, Autonomous Public Clinical Hospital No. 1
[d] Department of Diagnostic Imaging and Interventional Radiology

Pomorski Uniwersytet Medyczny w Szczecinie:
Studenckie Koło Naukowe przy Zakładzie Diagnostyki Obrazowej i Radiologii Interwencyjnej:
[a] dla studentów polskojęzycznych, [b] dla studentów anglojęzycznych
[c] Zakład Diagnostyki Obrazowej i Radiologii Interwencyjnej, Samodzielny Publiczny Szpital Kliniczny Nr 1
[d] Zakład Diagnostyki Obrazowej i Radiologii Interwencyjnej

ANATOMICAL DISORDERS OF GENITOURINARY SYSTEM IN CHILDREN WITH SIRENOMELIA IN DIAGNOSTIC IMAGING

Abstract

Introduction and aim: Sirenomelia sequence is a rare congenital malformation characterized with a single midline lower limb.
Material and methods: Information comes from available literature sources that were reviewed. The method of diagnostic imaging and theoretical analysis has been used.
Results: The group of the most common urogenital disorders occurring with sirenomelia includes renal dysplasia or agenesis and rudimentary genitalia. Sirenomelia is accompanied by a distinctive vascular anomalies, especially a single large umbilical artery, which arises above the aortic bifurcation and absence of inferior mesenteric artery which causes that the colon usually ends blindly, and moreover cardiac defects.
Conclusion: Internal organs with disorders occurring with sirenomelia should be examined in physical examination and using imaging methods, including ultrasounography and magnetic resonance of the fetus and the neonate.

Keywords: Sirenomelia, urogenital system, rare diseases, radiology.
(Received: 16.09.2016; Revised: 20.09.2016; Accepted: 25.09.2016)

ZABURZENIA ANATOMICZNE UKŁADU MOCZOWO-PŁCIOWEGO U DZIECI Z SYRENOMELIĄ W DIAGNOSTYCE OBRAZOWEJ

Streszczenie

Wstęp i cele: *Sirenomelia to rzadka sekwencja wad wrodzonych charakteryzująca się pojedynczą kończyną dolną zlokalizowaną w linii pośrodkowej ciała.*
Materiał i metody: *Informacje uzyskano w wyniku przeglądu dostępnych źródeł literaturowych. Zastosowano metodę diagnostyki obrazowej i analizy teoretycznej.*
Wyniki: *Do grupy najczęstszych zaburzeń układu moczowo-płciowego występujących z sirenomelią należą dysplazja lub agenezja nerek i szczątkowe genitalia. Sirenomeli towarzyszą anomalie naczyniowe, zwłaszcza pojedyncza duża tętnica pępowinowa, która bierze początek powyżej rozwidlenia aorty i brak tętnicy krezkowej dolnej, co powoduje, że jelito grube zazwyczaj kończy się ślepo, a ponadto wady serca.*
Wnioski: *Narządy wewnętrzne dotykane zaburzeniami występującymi z sirenomelią powinny zostać zbadane w badaniu fizykalnym i przy użyciu metod obrazowania, w tym ultrasonografii i rezonansu magnetycznego płodu i noworodka.*

Słowa kluczowe: *Syrenomelia, układ moczowo-płciowy, choroby rzadkie, radiologia.*
(Otrzymano: 16.09.2016; Zrecenzowano: 20.09.2016; Zaakceptowano: 25.09.2016)

1. Introduction and aim

Sirenomelia sequence is a rare congenital malformation characterized with a single midline lower limb. Incidence of sirenomelia sequence is between 1/60000 and 1/100000 [5] with male to female ratio being 3:1 [6]. Other anomalies associated with sirenomelia sequence are bilateral renal agenesis, sacral agenesis, genital defects, imperforate anus and cardiac defects [5]. The rarity of the case is obvious from the fact that many gynecologists might not have come across a case of sirenomelia in their whole professional career [6].

The pathogenesis of sirenomelia is not fully understood but is thought to be due to a signaling Bmp deficit in the embryonic caudal end, which has a role in vasculogenesis [4], [11] and due to excess of signaling retinoic acid (RA), which in mice has been found to be due to lacking of Cyp26a1, a RA degrading enzyme. Worth noting is that RA levels, besides genetic factors, can be influenced by nutritional factors and thus can be a cause of environmental sirenomelia [4].

Two hypotheses regarding the pathogenicity have been proposed. The first one known as the 'vascular steal hypothesis' refers to vascular hypoperfusion as origin of pathogenesis. It proposed that the malformation of the lower part of the body is due to diverted blood flow to the placenta by a single umbilical artery (SUA) of vitelline origin, instead of double as usual [4], [7], [11]. Deficient blood flow results in fused lower limbs and agenesis of midline structures. The presence of SUA of vitelline origin has been proposed as a differential diagnosis, differencing sirenomelia from other lower body malformations [4]. The second one known as the 'defective blastogenesis hypothesis' refers to primary defect in development of caudal body that occurs during the third gestational week in humans [4], [11].

Etiological factors of sirenomelia sequence are still unclear. Several heterogeneous risk factors have been reported, but all of them are debatable [5]. Possible maternal risk factors associated with sirenomelia are diabetes mellitus, tobacco use, retinoic acid, heavy metal exposure and young maternal age (under 20) [5], [6]. Maternal diabetes is reported in 2% of cases. Quite high percentage, as 15%, of sirenomelia cases are in twin births – most of them monozygous and only one fetus is affected. There is no clear environmental factor associated with sirenomelia sequence [5].

The most obvious symptom of sirenomelia is the dismorphic lower limbs, also accompanied with Potter's face and spade like hands which is classificated according to Stocker and Heifetz (Stocker and Heifetz, 1987) [11].

Tab. 1. Classification of sirenomelia (Stocker and Heifetz, 1987) [11]

Type:	Features:
I	all thigh and leg bones are present
II	single fibula
III	absent fibula
IV	partially fused femurs, fused fibulae
V	partially fused femurs
VI	single femur, single tibia
VII	single femur, absent tibia

The study was performed to gather information about patients with sirenomelia sequence scattered in medical literature giving statement on morphological disorders of genitourinary system and basic epidemiological data.

2. Material and methods

Presented information comes from available literature sources and was obtained as a result of the review of scientific articles on studied topic. The method of diagnostic imaging and theoretical analysis has been used.

3. Results

In virtually all instances, sirenomelia is accompanied by a distinctive vascular anomalies; a single large umbilical artery, which arises above the aortic bifurcation, is typical. The kidneys and the urinary tract drainage are absent or markedly dysplastic. The inferior mesenteric artery is absent and the colon usually ends blindly. Cardiac defects occur in many cases.

Tab. 2. Clinical data from exemplary patients with sirenomelia

Source of description	Maternal / gestational age (yr*/Hbd*)	Renal disorders	Sex / urogenital disorders	IA*	SUA*	Other major malformations
Stanton 2003	14 / 35	pelvic horseshoe kidney	f* / Y-shaped ureter, absent bladder, ureter opened directly onto the perineum, adjacent to a blind-ending vagina, absent uterus	yes	yes	dextrocardia and situs solitus with an acyanotic tetralogy of Fallot, multiple ventricular septal defects, moderately severe infundibular stenosis, cecum and appendix located in the left upper quadrant and liver in the midline, colonic and rectal agenesis
Garrido-Allepuz 2011	16 / 28	renal agenesis, oligohydramnios	m* / undescended testicles	yes	yes	dead fetus, sacral agenesis, hypoplastic pelvis, fused lower extremities with paired femurs and tibias, but absent fibulae, Potter's face, hypoplastic lungs
Ikbal 2012	34 / 34	bilateral renal agenesis	- / absent genitalia	yes	yes	single lower limb, absent fibula, bones of foot and digits, sacral agenesis, hemivertebra, Potter's face, anencephaly
Seidahmed 2014	32 / 36	absent kidney, oligohydramnios	- / absent genitalia, no bladder	yes	yes	Potter's face, microftalmia
Seidahmed 2014	23 / 31	absent kidney, oligohdramnios	- / absent genitalia	yes	yes	Potter's face, hypoplastic lungs, two chambers heart
Samal 2015	27 / 39	-	- / absent genitalia	yes	yes	hypertelorism, Potter's face, narrow chest, bilateral hypoplastic thumb, fused lower limbs with a single foot and 5 toes

Samal 2015	23 / 34	bilateral renal agenesis, very scanty amniotic fluid drained at the time of delivery (unsupervised pregnancy)	- / absence of ureters, urinary bladder, seminal vesicle, urethra and genitalia except two pea sized structures suggestive of testes (bilaterally posterior to pubis)	yes	yes	fused both lower limbs and feet with 10 toes (type I of Stocker and Heifetz classification), Potter's face, narrow chest indicating lung hypoplasia, right pneumothorax with collapsed right lung

* yr – years, Hbd – *(lat. hebdŏmăs)*, f – female, m – male, IA – imperforated anus, SUA – single umbilical artery

Tab. 3. Clinical data from 2 patients with caudal regression syndrome

Source of description	Maternal / gestational age (yr*/Hbd*)	Renal disorders	Sex / urogenital disorders	IA*	SUA*	Other major malformations
Seidahmed 2014	28 / in term	normal	f* / normal	no	no	no
Seidahmed 2014	30 / in term	left crossed ectopia, VUR (grade II)	f* / normal	no	no	neurodevelopmental delay, VSD, PDA

* yr – years, Hbd – *(lat. hebdŏmăs)*, f – female, IA – imperforated anus, SUA – single umbilical artery

4. Discussion and conclusions

Most common urogenital disorders include renal dysplasia, urethral dysplasia and total renal agenesis [2], [4], [9].

Renal atresia or hypoplasia, urethral agenesis and absence of genitalia, excluding the gonads, have been reported with variable frequency [2], [4], [9]. Ectopic renal tissue in the pelvis has also been reported [4]. Associated anomalies include sacral agenesis, anorectal atresia, imperforate anus, renal agenesis, absent urinary bladder, lumbosacral and pelvic bone abnormalities, ambiguous genitalia, and single umbilical artery [1].

Retrograde pyelography, performed at the same time as a perineal meatotomy showed pelvi-ureteric junction obstruction, with a short megaureter draining the pelvic horseshoe kidney [11].

Renal agenesis can be demonstrated using ultrasonography as it was done among others by Samal, Ikbal and their co-authors [5], [6].

Genital malformations or absence of genitalia are common however gonads are usually unaffected [2], [4], [11]. Ambiguous genitalia have been also reported [2]. In view of the inconsistencies in the definition of the term 'genitalia' ('genitals'), including only external or also internal organs of genital system, that term in this article is used only in the meaning of external genital organs in general. Internal organs of this system are mentioned by name.

Usually sirenomelia is diagnosed in the second trimester or even later due to the severe oligohydramnios caused by renal agenesis. In contrast, amniotic fluid could be reduced in the first trimester; it is formed by the amniotic membrane, thus making visualization of the fetus

easier at this gestation [1], [2]. Color Doppler ultrasonography can help in identifying single umbilical artery. Sirenomelia is unlikely if two umbilical arteries are seen [1].

Detailed evaluation of fetal anatomy of abdominal may not to be possible when gestation age is too low. The fetal bladder is almost always visible at the 12-week scan. Transvaginal scan is an excellent modality for imaging and should be performed at the first-trimester for better visualization of detailed anatomy. All four limbs should be well visualized and should be freely moving at the scan. It is recommended to plan postnatal evaluation by fetal X-ray and autopsy as it confirms the diagnosis, which is extremely important for patient counseling [1]. It is possible to detect sirenomelia in the first trimester, but it is very important to know the symptoms, for the reason that prevention and early diagnosis could help patients.

Abdominal and cranial magnetic resonance could not be performed when patient's condition is poor [5]. In one case magnetic resonance angiography delineated aorta tapering caudally and dividing as it extended into the fused lower limb segment [11].

Classical radiography, irrespective of whether intravital or post mortem, could be used to examine skeletal changes as it was shown in cases described by Garrido-Allepuz, Ikbal and their co-authors [4], [5].

Another issue important in the diagnostics and the process of treatment is to detect and describe disorder in other organs, e.g. holoprosencephaly, sometimes coexisting with sirenomelia, is diagnosed using transabdominal and transvaginal ultrasound examination of the fetus with possibility to control it through anterior fontanelle after birth, magnetic resonance of the fetus and the neonate or computed tomography of brain, if necessary [10].

It is valuable to perform imaging in every fetus and newborn with sirenomelia. As it was demonstrated most of patients have examinations of internal organs, but not all these that are usually affected.

At the end it is worth noting that there is an association between sirenomelia or caudal regression syndrome and VACTERL (vertebral, anal, cardiac, tracheo-esophageal fistula, renal and limb malformation) [12].

References

[1] Chanchal S., Pooja L., Deepshikha A., Akshatha P.S., Anita K.: *Diagnosis of Sirenomelia in the First Trimester*. Journal of Clinical Ultrasound, Malden 2014, 6(42), pp. 355-359.

[2] Chikkannaiah P., Mahadevan A., Gosavi M., Kangle R., Anuradha., Shankar S.K.: *Sirenomelia with associated systemic anomalies: An autopsy pathologic illustration of a series of four cases*. Pathology – Research and Practice, Stuttgart 2014, 210, pp. 444-449.

[3] Duesterhoeft S.M., Ernst L.M., Siebert J.R., Kapur R.P.: *Five cases of caudal regression with an aberrant abdominal umbilical artery: Further support for a caudal regression-sirenomelia spectrum.* American Journal of Medical Genetics. Part A, Hoboken 2007, 143A, pp. 3175-3184.

[4] Garrido-Allepuz C., Haro E., González-Lamuño D., Martínez-Frías M., Bertocchini F., Ros M.A.: *A clinical and experimental overview of sirenomelia: insight into the mechanisms of congenital limb malformations*. Disease Models & Mechanisms, Cambridge 2011, 4, pp. 289-299. doi:10.1242/dmm.007732.

[5] Ikbal M., Kahveci H., Aksoy B.A., Laloglu F., Kacmaz E., Alp M.Y.: *A case of sirenomelia sequence*. Pakistan Journal of Medical Sciences, Karachi 2012, 28(5), pp. 968-970.

[6] Samal S.K., Rathod S.: *Sirenomelia – The mermaid syndrome: Report of two cases*. Journal of Natural Science, Biology and Medicine, Cork 2015, 6(1), pp. 264-266.

[7] Schiesser M., Holzgreve W., Lapaire O., Willi N., Lopez R., et al.: *Sirenomelia, the mermaid syndrome-detection in the first trimester*. Prenatal Diagnosis, Chichester, New York 2003, 23, pp. 493-495.

[8] Seidahmed M.Z., Abdelbasit O.B., Alhussein K.A., Miqdad A.M., Khalil M.I., Salih M.A.: *Sirenomelia and severe caudal regression syndrome*. Saudi Medical Journal, Riyadh 2014, 35(12), pp. 36-43.

[9] Sirtori M., Ghidini A., Romero R., Hobbins J.C.: *Prenatal diagnosis of Sirenomelia*. Journal of Ultrasound in Medicine, Rockville 1989, 8, pp. 83-88.

[10] Skoczylas M.M., Wełnicka A., Kulig M., Sawicki M., Donotek M., Walecka A., Rudnicki J.: *Przodomózgowie jednokomorowe i syrenomelia oraz ich współwystępowanie jako wyzwanie diagnostyczne i terapeutyczne*. Postępy Neonatologii, Warszawa 2014, 2(20), pp. 89-92.

[11] Stanton M.P., Penington E.C., Hutson J.M.: *A surviving infant with sirenomelia (Mermaid Syndrome) associated with absent bladder*. Journal of Pediatric Surgery, Philadelphia 2003, 38, pp. 1266-1268.

[12] Szumska D., Pieles G., Essalmani R., Bilski M., Mesnard D., Kaur K., et al.: *VACTERL/caudal regression/Currarino syndrome-like malformations in mice with mutation in the proportion convertase PcsK5*. Genes and Development, Woodbury 2008, 22, pp. 1465-1477.