Sirenomelia - Mermaids Out of the Sea – Report of 3 Cases from Kerala, India, with Review of Literature

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ABSTRACT

BACKGROUND

Sirenomelia or mermaid syndrome is a rare and fatal congenital multisystemic anomaly characterised by different degrees of fusion of lower limbs, thoracolumbar spinal anomalies, sacrococcygeal agenesis, genitourinary and anorectal atresia. It is more common in foetuses of diabetic mothers and monozygotic twins. Approximately 300 cases have been reported in the literature and very few have been reported from this subcontinent. Although, this syndrome is incompatible with life due to the association of several congenital visceral abnormalities, there have been nearly nine reported sirenomelia affected cases, who have survived after multiple reconstructive surgeries. The most important factor for survival of affected new-borns was functional kidney.

METHODS

All foetal autopsy cases received over the past 5 years in the Department of Pathology, Trivandrum Government Medical College were analysed with special emphasis on sirenomelia (mermaid syndrome). The clinical history, post-mortem x-ray, and gross evaluation of these sirenomelia babies were studied in detail.

RESULTS

There were 3 cases of sirenomelia out of 14 cases associated with syndromes during the study period. The cases encountered had various known risk factors and different degrees of lower limb fusion, as mentioned in the literature.

CONCLUSIONS

Congenital anomalies are on the rise as a cause of fetal death. Fetal autopsy correlates well with prenatal ultrasound and karyotyping. It provides added information in a significant number of cases. Sirenomelia is a rare congenital anomaly where early detection by prenatal ultrasound will help in timely management of pregnancy. Genetic & prenatal diagnosis would ensure an optimal management from psychological and health cost point of view. This case series emphasises the need for perinatal autopsy for all cases of foetal death.

KEYWORDS

Foetal Autopsy, Sirenomelia, Mermaid Syndrome, Caudal Regression Syndrome

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BACKGROUND

The study of the dead enriches the knowledge of life and death, which can be accomplished by autopsy. Autopsies in general have their roots from the end of the thirteenth century.[1] The approach to perinatal autopsy is not the same as in adult autopsy.[2] The diseases and conditions considered in the foetus are not the same as that encountered in adults. The perinatal autopsy is a multidisciplinary effort involving the obstetrician, radiologist, pathologist, paediatrician and a geneticist.[3] The pathologist in general, has a growing responsibility of documenting and reporting anomalies for genetic counselling, providing epidemiological data and stimulate research. Several studies have been conducted worldwide including India. Such studies were conducted to provide valuable information about the frequency and distribution of congenital anomalies and important clues to the early diagnosis, prevention and treatment. Autopsy facilities are still primitive in India[1]. This study focuses on one such rare congenital malformative disorder seen in foetuses called sirenomelia. This disorder is extremely rare and often fatal,[4] with an incidence of about 1 in 100,000 pregnancies.[5] This disorder is also known as the mermaid syndrome which was described by Rocheus in 1542.[6] The most characteristic yet inconstant feature of this malformative disorder is the complete or partial fusion of the lower limbs into a single lower limb.[7] The infant bears a resemblance to the mermaid of ancient Greek mythology.[8]

Around 300 cases have been reported in the world literature, of which only 13 have been from India. We hereby report three cases of sirenomelia that were received in the department in five years. This case series is one of the largest in Indian literature. This was undertaken with a view to study the incidence of congenital malformations in perinatal death in general, analyse the utility of histopathology in the cause of death, discuss the findings in relation to the present literature and related controversies of its etiopathogenesis.

Objectives

To find out the incidence of congenital anomalies detected in perinatal autopsies, to study in detail about sirenomelia (mermaid syndrome) babies with respect to the risk factors, the various anomalies present in them and their outcome.

METHODS

This was a retrospective descriptive study where all foetal autopsy specimens received in the Department of Pathology, Government Medical College, Trivandrum over a period of five years from January 2009 to December 2013 were analysed. The cases of sirenomelia babies received during this study period were studied in detail. Relevant clinical history and post-mortem x-rays were obtained. The specimens were grossed according to the standard autopsy protocols, haematoxylin & eosin stained tissue sections were studied and a detailed literature review was done.

RESULTS

Of the 440 fetal autopsies received in the department during the study period, 23.4 % of cases (103 cases) had congenital anomalies [Table 1]. Most of the cases had multiple anomalies involving different organs (38 / 103 cases). On further analysis, the most common system to be involved was the gastrointestinal tract followed by cardiovascular system and genitourinary system. There were 14 cases associated with syndromes, among them sirenomelia (mermaid syndrome) was seen in 3 cases.

Year	No. of Fetal Autopsies	Male	Female	Ambiguous Genitalia	Total No. of Congenital Anomaly Cases
2009	99	12	14	1	27
2010	105	11	13	-	24
2011	107	11	11	1	23
2012	83	6	10	-	16
2013	46	4	7	2	13
Total	**440**	**44**	**55 (53 %)**	**4**	**103 (23.4 %)**

Table 1. Frequency of Congenital Anomaly Cases in Fetal Autopsy Specimens

Case 1

A 32-year-old healthy multigravida lady with monochorionic monoamniotic (MCMA) twins at 30 weeks + 1 day of gestational age was referred to our institute with history of preterm labour pains. She had a normal antenatal course with an ultrasound scan done two months ago revealing MCMA twin gestation (one cephalic and the other in breech presentation). Her oral glucose tolerance test (OGTT) was abnormal. She had a previous normal delivery, and the child was healthy. There was no history of drug intake, radiation exposure or history of maternal diabetes mellitus. On admission, her vitals were stable. On examination, she was found to be in second stage of labour with uterine size of 34 - 36 weeks, had mild contractions and good fetal heart sounds. Her routine blood investigations were normal. Ultrasound scan on admission showed MCMA twin fetuses. The 1st fetus had an estimated gestational age of 29 weeks + 1 day with cephalic presentation and an estimated weight of 1370 gms. The 2nd fetus had poor definition of fetal parts and no cardiac activity. Femur length was 46.6 cm corresponding to 25 weeks + 4 day. There was severe oligohydramnios. Placenta was normal in position. She underwent spontaneous preterm twin vaginal delivery.

The 1st twin was a preterm male baby of 1.4 Kg with poor Apgar score and was shifted to neonatal intensive care unit (NICU) for observation. His monozygotic twin was an intrauterine demise (IUD) baby. Immediate postnatal examination revealed a macerated and anomalous baby of 880 gm. Placenta and membranes were delivered in-toto. The IUD baby was sent for autopsy examination.

The external anomalies noted were a single inferior limb, imperforate anus, absence of external genitalia and urinary meatus, distended abdomen and single umbilical artery [Figure 1a & b]. The baby also had features of Potter's facies and anomaly of the left arm. Post-mortem radiographic images revealed multiple skeletal anomalies like sacral agenesis, vertebral dysgenesis at L4 - L5 level and single

femur, thus classifying our patient as Type VII of Stocker and Heifetz classification of sirenomelia sequence which is the most severe form [Figure 2]. Abdominal ultrasonography was not performed. Internal anomalies included a blind bowel with absence of rectum, right renal agenesis with left hydronephrosis, tubular bladder, absent gonads and single umbilical artery [Figure 3]. Other internal organs were normal.

Figure A.
Sirenomelia Baby with Single Lower Limb, Absent External Genitalia and Urinary Meatus, Left Anomalous Hand & Potter's Facies

Figure B.
Imperforate Anus

Figure 1. External Anomalies

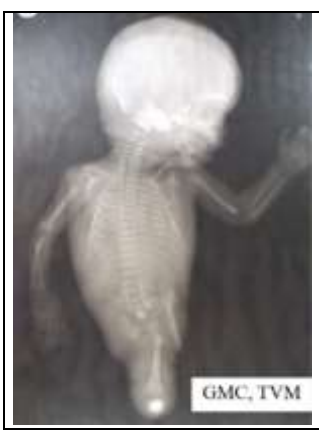

Figure 2.
Radiographic Features

Single femur with absence of tibia and fibula and sacral agenesis.

Case 2

A 21-year-old unbooked primigravida at 38 week + 6 days of gestational age presented with spontaneous labour pains. Her routine blood investigations and serum viral markers were normal. Her blood group was A negative. Ultrasound scan on admission showed a single live intrauterine fetus of 27 weeks + 2 days of age with breech presentation, poor biophysical profile, inadequately sustained fetal cardiac activity, overlap of fetal parts and non-visualisation of femur. She delivered a stillborn and anomalous baby by normal vaginal route. At fetal autopsy, external examination revealed Potter's facies, distended abdomen, undetermined sex, imperforate anus, absent urinary meatus and fused lower limbs [Figure 4A]. Radiographic images showed 2 femur, 2 tibia and 2 fibulae thereby classifying this case as Type I of Stocker and Heifetz classification of sirenomelia sequence [Figure 5]. Internal examination revealed atrial and ventral septal defects (ASD; VSD) [Figure 4B], absent thymus, kidney & adrenals and bilateral congenital cystic adenomatoid malformation type III.

Figure 3A.
Sirenomelia Baby with Fused Limbs Resembling Mermaid and Absent Genitalia

Figure 3B.
Internal Examination Shows Heart with Atrial Septal Defect

Figure 3. External and Internal Anomalies

Figure 4.
Radiographic Features

Post-mortem radiographic images showing fused limbs with 2 femur, tibia and fibula each.

Case 3

A 25-year-old primigravida patient delivered a severely anomalous intrauterine dead fetus at 35 weeks + 4 days of

gestational age. She was referred to our institute with history of decreased fetal movements and labour pains. Her antenatal investigations revealed maternal diabetes. Previous ultrasonographic findings were not available at the time of admission. There was no other significant personal, drug or medical history. On admission, her vitals were stable and complete blood count was normal. She was found to have significantly elevated random blood glucose levels (210 mg / dl). Oral glucose tolerance test (OGTT) could not be performed as patient was in active labour. Ultrasound scan on admission showed severe oligohydramnios and an intrauterine fetus of 30 weeks of age with absent cardiac activity. Immediate postnatal examination revealed a macerated and anomalous baby of 1100 gm. Fetal autopsy revealed malformed ears with no auditory meatus, absent external genitalia, imperforate anus and single umbilical artery. There was a single lower limb [Figure 6A]. Radiographs revealed sacral agenesis, single limb with one femur, one tibia and absent fibula corresponding to Type VI of Stocker and Heifetz classification of sirenomelia sequence [Figure 6B]. Internal malformations included oesophageal and duodenal atresia, absent gonads & right kidney and a blind tubular bladder.

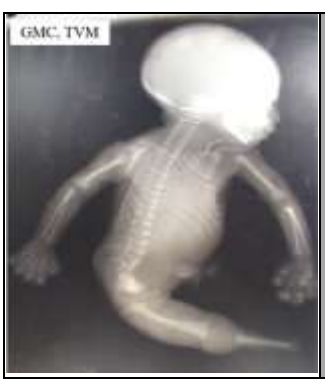

Figure 5. Radiographic Features

DISCUSSION

Sirenomelia or mermaid syndrome is abnormal development of the caudal region of the body involving varying degrees of fusion of the lower limbs with or without bony defects.[9] The first medical description of sirenomelia was reported way back in sixteenth century by Rocheus and Polfyr. In 1961, Duhamel defined all the anomalies of mermaid syndrome and described it as the most severe form of caudal regression syndrome.[10] Before publication of Stevenson's studies about sirenomelia pathological features in 1986, all caudal extremity development anomalies were grouped under the term caudal regression syndrome (CRS) or sirenomelia sequence. This condition was characterised by a spectrum of abnormalities ranging from anal imperforation in its most mild form to full sirenomelia with fusion of the two lower limbs, which constituted as the most severe form. Sirenomelia is usually associated with other visceral defects such as hypoplastic lungs, cardiac agenesis, absent genitalia, digestive defects, absent kidney & bladder, vertebral and central nervous system defects.[11,12] Oligohydramnios secondary to severe renal dysplasia is universal. Death usually results from obstructive renal failure due to renal agenesis or dysgenesis, with survival depending on adequate kidney functioning and renal outflow.[13]

Risk Factors & Aetiopathogenesis

The aetiology of this multisystemic congenital malformation is unknown and no teratogenic agents have been found in humans.[14] Certain risk factors however exist. Maternal diabetes is one such important risk factor for caudal malformations in general[9]. However, with only about 0.5 – 3.7 % of sirenomelia cases occurring in diabetic mothers, the association is described as weak. Two of our cases were born to diabetic mothers. The other known risk factor was that 9 - 15 % of sirenomelia cases were reported to be associated with twin pregnancies with 100 – 150 times higher incidence in monozygotic twins relative to dizygotic twins or singletons.[15] In our case series, there was a monozygotic twin gestation.

It is worth noting that although Lynch et al.[16] recognised an autosomal form of caudal dysgenesis, no chromosomal abnormalities were found in sirenomelia and it does not recur in families[11]. This was a reassuring feature for our patients and should serve as a counselling feature for mothers bearing babies with this distressing anomaly. Though teratogens like retinoic acid, cadmium and cyclophosphamide have been implicated in the genesis of sirenomelia in mice and hamsters,[17,18] no case of sirenomelia in humans has been observed after incidental maternal exposure to these products.

Numerous theories have been proposed to explain the origin of this rare disorder. The two main pathologic hypotheses namely, the vascular steal hypothesis and defective blastogenesis hypothesis were proposed. Stevenson et al.[19] proposed the vascular steal theory which suggested that there was shunting of blood via an abnormal abdominal artery arising from high up in the aorta towards the placenta. This leaves the caudal part of the embryo poorly perfused. Jaiyessimi et al.[20] reported a case of sirenomelia without this vitelline artery steal, indicating that factors other than vitelline artery steal could be responsible for sirenomelia in humans. Bohring et al.[21] postulated that the spectrum of congenital malformations observed in caudal regression syndrome (CRS) represents abnormalities in blastogenesis and is due to disturbances of a primary embryonic field. The defective blastogenesis theory regards sirenomelia as part of the caudal regression syndrome (CRS), more recently referred to as caudal dysgenesis.[7,10] Even though the syndrome was initially described by Duhamel[22] to include genitourinary and vertebral anomalies, phenotypic expression depends on the intensity, duration and initiation time of the underlying event.[7] Some authors consider sirenomelia to be the most extreme form of this relentless condition. A further theory described in the literature regards sirenomelia as part of the VACTERL syndrome. VACTERL syndrome involves vertebral, anal, cardiovascular, tracheoesophageal, renal and limb dysgenesis. There was a major overlap in the phenotypic manifestations of sirenomelia and VACTERL.[18] In most cases, the distinction between sirenomelia sequence and

VACTERL lies within the severity of the component defects, and the single lower limb in sirenomelia can be regarded as an indicator of other severe malformations, especially in the gastrointestinal and genito-urinary systems.

Genetic Aspects

Recently, sirenomelia-like phenotype has been observed in several genetically modified mouse strains with either gain-of-function of retinoic acid (RA) signalling or loss-of-function of bone morphogenetic protein (Bmp) signalling. Bmp performs multiple important roles during early embryogenesis, including the control of gastrulation and plays a crucial role in angiogenesis and vasculogenesis by promoting endothelial cell activation, migration and proliferation, three processes that are central to the establishment and remodelling of the vasculature.[23] Similar to Bmp, RA signalling also plays crucial roles during early embryogenesis, particularly in influencing the development of caudal structures. The spatiotemporal distribution of RA in the early embryo is tightly controlled by the balanced expression of its synthesising and catabolising enzymes. The expression of Cyp26a1, which occurs at the early gastrula stage in the primitive streak and its newly formed mesoderm, shifts to the open neuropore, hindgut endoderm and tailbud mesoderm at the late gastrula stage, where it participates in the caudal development of the embryo.[24] Sirenomelia occurs when RA signalling is increased in the caudal end of the embryo. Increasing RA levels act by decreasing Bmp signalling levels.[23,24]

Classification

Stocker and Heifetz[9] classified the sirenomelia sequence into 7 types as shown in Table 2. They were classified according to the presence of skeletal elements in the thigh and leg. In type I, the mildest form, all bones in the two fused limbs are present and in type VII, the most severe form, only a single bone is present, with no indication of legs or feet.

Type	Characteristics
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

Table 2. Stocker and Heifetz's Classification of Sirenomelia

Diagnosis

The past medical history of the patient could identify the patient at risk. Antenatal diagnosis is possible with ultrasonographic and x-ray findings. Sirenomelia can be diagnosed by sonography as early as 9 weeks. In sirenomelia foetuses, bilateral renal agenesis causes severe oligohydramnios thus limiting ultrasound evaluation of the limbs in the second and third trimesters. Ultrasound features permitting confirmation of the diagnosis include lack of tibia / fibula, a single femur, convergent femoral bones, bilateral renal agenesis, polycystic kidneys / renal agenesis, obstructive uropathy and intra-uterine growth retardation.[22] Other abnormalities may involve the cardiovascular system and abdominal walls. Diagnosis can be confirmed by high-resolution sonography by presence of continuous skin line over both femurs on a transverse scan of the thigh, indicating fused thighs. Colour Doppler sonography reveals the origin of the aberrant vitelline artery that continues as the single umbilical artery. All our cases were diagnosed after birth and no definite antenatal diagnosis was possible.

Antenatal confirmation of the diagnosis justifies a therapeutic termination of the pregnancy when permissible. At delivery, clinical evaluation is usually sufficient to confirm the diagnosis. It seems justifiable to insist on the screening of sirenomelia in diabetic women along with the screening of diabetes in pregnant women. An autopsy permits determination of the extent of the associated anomalies but could limit its use in the Asian context where cultural norms and beliefs largely precludes its practice.

Management & Prognosis

Sirenomelia carries a very poor prognosis and survival is largely dependent on the extent of visceral anomalies, especially obstructive renal failure and pulmonary hypoplasia.[25] The management of sirenomelia is difficult and expensive, and the outcome is unpredictable. Initial treatment includes supportive care and diverting colostomy. Owing to visceral abnormalities, sirenomelia is usually incompatible with life; death occurs in the perinatal period. Recent reports indicate that about 50 % of these infants are born alive after 8 – 9 months gestation.[25] A few exceptional cases have survived owing to the presence of a functional kidney and reconstructive surgery to restore pelvic organs and separate the legs. The babies who survived had normal neurological development. The main therapeutic modality involved surgical and medical interventions aimed mainly at maintaining adequate renal function. Voluntary termination of pregnancy is advisable to avoid the physical and psychological stress to the family. This decision however depends on the gestational age of the pregnancy, the severity of the malformations and of course the desires of the parents.[10] There have been reports of surviving fetal sirenomelia cases.[26-30] In the case described by Stanton,[26] the patient had five interventions between the age of 15 days and 4 years; she continues to be bedridden and dependent. Surgery to correct the anomaly and separate the fused limbs is usually not a priority as there is no guarantee of its success and it carries with it an increased risk of compromising the life of an already delicate infant. There are lot of financial and physical constraints to conservatively manage sirenomelia.[31-34] Hence, this study reiterates the importance of antenatal diagnosis and voluntary termination of pregnancy especially in resource limited settings like ours. Genetic counseling should be proposed because the estimated risk of reoccurrence is 3 % – 5 %.[14]

CONCLUSIONS

Sirenomelia is a rare and peculiar congenital anomaly. Controversies on its aetiopathogenesis persist. Antenatal diagnosis is possible by ultrasound. The associated visceral anomalies are usually incompatible with life. However, surviving fetal sirenomelia cases have been described with costly conservative management and mediocre results. Regular antenatal check-up with optimum maternal blood glucose level in pre-conceptional period and in first trimester should be maintained to prevent this anomaly. In certain parts of the world, these mermaid babies carry with them the connotation of sorcery and witchcraft with which no family wishes to be identified. Knowledge of this rare syndrome is important to dissipate cultural myths whenever it occurs, and free the family from stigmatisation. Therefore, there must be emphasis on the early detection to ensure an optimal management that would consequently be less demanding both from a psychological and health point of view.

The present study concludes that perinatal foetal autopsy is an important and valuable tool in determining the cause of death and in the identification of congenital anomalies. Promptness from the clinicians and pathologists is essential for an accurate diagnosis. Congenital anomalies are on the rise as a cause of death, due to improvements in the ultrasound facilities along with antenatal care, labour room facilities and neonatal care. Surveillance of congenital anomalies can help in better antenatal screening practices and in identifying the social and regional pattern of congenital malformations. Autopsy correlates well with prenatal ultrasound and karyotyping and in addition provides added information in a significant number of cases. Hence, perinatal autopsy should be carried out.

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