CONGENITAL LIMBS DEFICIENCY VERSUS PHOCOMELIA THE HARD WORKUP WITH THE SUBTLETIES AND MALFORMATIONS ACCOMPANYING THE SYNDROMES IMAGES; CASE SERIES

Mohammed J Aboud 1,a, Shaimaa M Kadhim b, Noor M Abudi c, Haidar M Joudi d and Zeena M Joudi d

1 Pediatric surgery unit, the Maternity and Child Teaching Hospital, Al Diwaniya, Iraq , b Department of pediatrics, the Maternity and Child Teaching Hospital, Al Diwaniya, Iraq , c Department of surgery, Al Diwaniya General Teaching Hospital, Al Qadisiya, Iraq , d Graduated doctor, College of Medicine, Al Qadisiya University, Iraq

ABSTRACT Background: Limb Deficiencies syndrome (LDS) is a spectrum of abnormalities present at birth. LDS are missing or incomplete limbs at birth. LDS can be Longitudinal (more common) or transverse deficiencies that involve specific mal developments. Splint hand foot malformation (SHFM) is one of the images of these deficiencies. LDS has been reported in conjunction with more than 75 genetic syndromes. Objective: We reported the conflicting images of these two rare malformations to claim knowledge about the presentation, having features of both critically associated anomalies, and the workup consideration with the treatment options. Presentation: CASE 1: a 2-day-old female neonate born at full term through Cesarean delivery at the 37th week of gestation presented with persistent cloaca. The patient was noted to have deformities resembling a “lobster claw” to both her feet; each hand had only a single digit; the foot may not have all five toes; the right leg is shorter than the other (a leg length discrepancy) with stable hips. CASE 2: a 37-week gestation male infant was born via cesarean section to a 32-year-old mother (consanguineous marriage). A routine prenatal ultrasound study revealed images of relatively undeveloped limbs and pelvic bones with an accumulation of spinal fluid under the skull (hydrocephalus). On initial assessment, the infant was noted to have facial abnormalities, Shortened neck, and eyes pointed downward. Images of phocomelia were suggested. Conclusion: LDS and phocomelia are very diverse in their epidemiology, aetiology, and anatomy and usually require a low threshold and careful intervention to improve functional and aesthetic outcomes. Physicians and caregiver should assign their workup precisely for the evaluations following initial diagnosis, prevention of primary manifestations, and prevention of secondary complications.

KEYWORDS Limb deficiency, phocomelia, malformations, images.

Introduction

Limb Deficiencies syndrome (LDS) is a spectrum of abnormalities present at birth. These abnormalities are attributed to the process of vascular disruption in limb structures that had formed normally and included defects referred to as the amniotic band syndrome [1]. LDS are missing or incomplete limbs at birth. LDS can be Longitudinal (more common) or transverse deficiencies that involve specific mal developments (e.g., complete or partial absence of the radius, fibula, or tibia) [2]. Radial ray deficiency is
the most common upper-limb deficiency, and hypoplasia of the fibula is the most common lower-limb deficiency. Splint hand foot malformation (SHFM) is one of the images of these deficiencies, characterized by the absence of certain fingers and toes (ectrodactyly) that suggest a claw-like appearance and webbing of fingers and toes may be present [2, 3]. It can be inherited as a single abnormality or as a part of a syndrome, which includes other characteristics. There are various symptoms and genetic causes of SHFM, and there can be varying levels of severity in affected people; severity can vary even among members of the same family [4]. The prevalence reports range from 0.1-0.5 cases per 10,000 births; however, the exact incidence is still unknown. LDS has been reported in conjunction with more than 75 genetic syndromes; it also has been reported in patients with VACTERL (associated vertebral, anal, cardiac, oesophageal, renal/kidney, limb, and growth defects) and Cornelia de Lange syndrome [5].

Anorectal malformations (ARMs) represent a common pathology that occurs in approximately 2-5 per 10,000 live births. ARM phenotypes include a spectrum of symptoms from benign to severe (complex), such as cloaca, which may also be categorized under the urorectal septum malformation sequence (URSMS) [6]. These symptoms may be associated with several diseases, such as the VACTERL complex. Phocomelia is an abnormality in which the limbs are not fully formed; usually, this malformation affects the normal growth and development of the musculoskeletal system and sometimes can be associated with craniofacial malformation, thoracic dysstrophy, and genital malformations like micropenis and cryptorchidism [7]. Etienne Geoffroy Saint first coined the term Phocomelia in 1836. It is not uncommon in undeveloped countries, and its prevalence is about 1 in 100,000 births. It may be inherited as an autosomal recessive or dominant disorder [8].

We reported the conflicting images of these two rare malformations to claim knowledge about the presentation, having features of both, critically associated anomalies, and the workup consideration with the treatment options.

Case Presentation

Case 1:
A 2-day-old female neonate born at full term through Cesarean delivery at 37th week of gestation and was the second born of non-consanguineous healthy young parents, presented with Imperforate anus with imperforate vagina, and the urethral opening was unclear; she was passing stool from the vestibule. The parents and the sibs show no deformities of any kind. There was no history of medication, alcohol intake, smoking, fever, or viral disease during pregnancy. Apgar scores 7/9 and 9/9 at 1 and 5 minutes, respectively. Weight, 3,010 g (50th percentile). Head circumference, 31 cm (25th percentile). Length, 50 cm (> 90th percentile). Local examination revealed the presence of persistent cloaca [figure 1, A].

Cardiovascular: Regular rate and rhythm, 2/6 systolic ejection murmur heard along left sternal border. The patient was noted to have deformities resembling a "lobster claw" on both her feet. Each hand had only a single digit [figure 1, B, C, D, & E]. The foot may not have all five toes; the right leg is shorter than the other (a leg length discrepancy) with stable hips. Despite limb-length shortening and alterations in limb alignment and stability, normal active mobility of both limbs was observed. The first ultrasonography study performed in the 26th week of gestation revealed a single fetus. A repeat sonographic examination at 32 and 34 weeks showed oligohydramnios, as-


cites, cystic tumor in the abdomen, difficulty visualizing the bladder, and mild bilateral hydronephrosis. However, antenatal ultrasound detected bilateral hydronephrosis, but we could not palpate the kidneys. For faecal diversion, a double-hole colostomy was created in the transverse colon, and drainage of hydrocolpos was performed; the perioperative course was uneventful. Postoperatively the baby arranged for more systemic investigations. Blood, electrolytes profiles, and thyroid function test within normal range. 2D-Echocardiogram study revealed moderate patent ductus arteriosus (PDA) and small ventricular septal defect (VSD) with mild bilateral ventricular hypertrophy. Baby roentgenogram [figure 2, A, B, & C] and Magnetic Resonance Imaging (MRI) were applied to evaluate the pelvic components and contour [figure 3, A]. Re ultrasonography reported rudimentary ovaries (volume less than 0.5 cm3), bilateral hydronephrosis, neurogenic bladder with residual urine (approximately 75 ccs) in the bladder, and right vesicoureteral reflex; it was a grade 5 on the VCUG study, [figure 3, B, & C]. Diuretic Reno gram (135MBq Tc99m MAG3) submitted poor function of the right kidney [figure 3, D]. Based on clinical evaluations and findings, Fanconi anaemia, VACTREL association, Thrombocytopenia absence radius syndrome, Holt-Oram syndrome, Townes-Brocks syndrome, and Roberts syndrome were suggested as a deferential diagnosis. The patient arranged for karyotyping and chromosomes studies; the images revealed abnormal female karyotype 46, XX, [figure 3, E]. During the period of serial follow-up, a paediatrician, pediatric surgeon, urologist, and gynaecologist multidisciplinary team arranged for her subsequent cloacal repair and managed the underlining urological anomalies. Orthopaedics clinic assessment was kept to maintain the surveillance and treatment program.

Case 2:
A 37-week gestation male infant was born via cesarean section to a 32-year-old mother (consanguineous marriage) with G3 P2+1, a weight of 3.5 Kg, with an Apgar score of 6/10 in one minute, and 9/10 in five minutes. There was no history of antenatal infections, and the mother had been taking oral Dydrogesterone and 75 mg Aspirin Tablets daily for possible threatened abortion in the early three months of the pregnancy. A routine prenatal
Figure 2 A, B, and C: A, and B; hands revealed a single digit in both hands with three metacarpals, with radial aplasia of the right one. C: feet showed bilateral deformity with only two digits, with right fibular aplasia.

Figure 3 A, B, C, D, and E: A; sagittal MRI shows a markedly distended vagina, compressed urinary bladder, and dilated uterus. B, and C; AP& lateral voiding cystourethrogram VCUG study revealed severe right vesicoureteral reflex. D; Diuretic Reno gram (135MBq Tc99m MAG3) submitted poor function of the right kidney; split function was 16.67%. E; Fluorescence in situ Hybridization (FISH) based karyotyping, the images revealed abnormal female karyotype 46, XX, with chromosome deletion in the long arm (the proximal breakpoint appeared to be in a band (Xq 22,3-25).

ultrasound study revealed images of relatively undeveloped limbs and pelvic bones with an accumulation of spinal fluid under the skull (hydrocephalus). On initial assessment, the infant was noted to have facial abnormalities, Shortened neck, eyes pointed downward (down-slanting palpebral fissures), and head circumference measures about (52cm). He has shortened arm and leg (hypomelia), with alterations in the alignment and stability of the limbs; just normal active mobility of both upper limbs was observed [figure 4, A, B, C, D, E, & F]. The neonate must be followed up by pediatric health care professionals and multi-speciality departments. Blood count profiles were within normal apart from the low platelets count (90,000 per microliter), thromboplastin time (15 seconds), and partial thromboplastin time (45 seconds). Baby roentgenogram reported a large-looking skull, with evidence of caudal regression [figure 5, A]. Abdominal US reported right hydro nephrotic ectopic kidney, giant liver mass (hemangioma), [figure 5, B], and large bowel content left inguinal hernia sac. Brain US revealed grossly dilated horns of lateral ventricles. An echocardiogram revealed a large ASD with a left to right shunt with an upper normal left ventricle thickness range. Images of phocomelia were suggested. After 2 months, he arranged for Computerized Tomography Scan (CT) for the brain; the report highlighted evidence of marked dilatation of the ventricles, especially the lateral and third ventricles [figure 5, C]. MRI study images of the spine revealed signs of caudal regression syndrome. Diuretics’ Reno gram revealed the preserved function of the left kidney and poor function of the right ectopic one [figure 5, D]. Hepatobiliary HIDA scan reported normal liver aspect functions [figure 5, E, & F].

Figure 4 A, B, C, D, E, and F: A; image revealed hydrocephaly, facial abnormalities, Shortened neck, hypertelorism, small nostrils, microretrognathia and abnormal ears. B; port wine stain facial hemangioma involving the anterior bridge of the nose and upper lip. C&D; the left leg appeared more shortened and bowed anterolateral, and an ipsilateral equinovalgus foot was present. E; partial cleft palate (white arrow). F; bilateral cryptorchidism (white arrow) with soft tissue swelling over the left lower quadrate and the left inguinal area (black arrow) extended to the left lumbar area (lumbar and left direct inguinal hernia).

Discussion
A congenital anomaly is an abnormality present at birth, even if not diagnosed until months or years later. Most congenital anomalies are present long before the time of birth, some in the embryonic period (up to the end of the seventh week of gestation) and others in the fetal period (eighth week to term).
Clinical Presentation, Pathophysiology, The distal portion of the limb bud of the developing embryo, consists of a cluster of cells known as the apical ectodermal ridge (AER) [13]. These cells produce signalling factors influencing the underlying mesenchyme to proliferate and differentiate into all limb skeletal elements. Patients with SHFM fail to maintain their AER, leading to the absence of phalanges, metacarpals, and metatarsals. Elliot and Evans describe a group of patients with SHFM. The latter also has been associated with congenital heart defects, including atrial septal defect, Tetralogy of Fallot, patent ductus arteriosus, and ventricular septal defect [13, 14]. However, in our first case, features of URSMS and VACTERL association overlap; we could not categorize this case under precise syndrome, she has a normal oesophagus and vertebrae, and the other syndromes criteria did not conclude the exact image of the related syndromes pathologies. This may state a limitation for the advanced map of the future workup and siblings’ expectations during parents’ genetic counselling. Carriers of balanced X, autosome translocations, and inversions, in whom the breakpoints range from the distal end of Xq13 to the distal end of Xq26, suffer from ovarian dysgenesis [15]. Accordingly, our first patient arranged as a part of the further workup for sex steroid estrogen, Follicular stimulating hormone (FSH), and luteinizing hormone (LH) assessments to roll out any dysgenesis or expected non-functional ovarian tissues (FSH & LH all over the normal range). Due to the considerable phenotypic variability of LDS, the announcement of the exact genotype-phenotype correlation is difficult. Lack of advanced resources, e.g. the molecular basis and the microarray facilities, made another limitation for the management team to claim the exact locus that determines and regroups all the associated malformations, in this case, in a generic term.

Nevertheless, the presence of associated abnormalities may allow a diagnosis of a recognized syndrome. There are varying reports on these frequencies; Calzorali et al. (1990) estimate 12%, with half-representing known syndromes [15, 16]. Future research on interactions of genes and their genetic and epigenetic control may help to pick up the background of the pathogenesis and phenotypic variability of such presentation of LDS.

Phocomelia ("Phoco" means seal" and "melia" means limbs) is a rare condition that affects babies at birth. This condition causes the upper or lower limbs of the child to be underdeveloped or missing [8, 17]. Phocomelia can affect one or multiple limbs and causes the limbs and appendages to be compressed or not develop. In some cases, fuses the fingers as well; only in extremely rare cases are there malformations of the face or cranium. This condition can be caused by a genetic syndrome; the National Organization for Rare Disorders (NORD) states an "irregular number of chromosomes" may be the cause or from exposure to a specific drug during pregnancy, substance use, like alcohol or cocaine, X-ray exposure, gestational diabetes, and blood flow problems [15, 17]. It goes by different names, including pseudo-thalidomide syndrome and Roberts SC-phocomelia syndrome. Phocomelia may be classified into three main types: complete, proximal, and distal. The other associated conditions categorized Phocomelia into; Sporadic Phocomelia, Holt-Hormam Syndrome, DK Phocomelia Syndrome, Schnitzel-Type Phocomelia, and CHILD Syndrome [8, 19, 20]. When such a case is identified in a child, the management team should thoroughly search for other associated abnormalities, as other defects are present in approximately half of the patients presenting with this limb anomaly. The team should assess the musculoskeletal system, including the vertebrae, the intestines, and the heart, as dysfunction in these organ systems appears most frequently in conjunction with phocomelia. Our second case carried images compatible with categorizing the baby under this pathology. However, other minor criteria may be missed (no one is affected in quite the same way, but there are similarities
to this condition). Authors submitted that 36.9% of phocomelia cases have additional major malformations, with 9.9% of cases being attributable to various syndromes [21, 22]. Major criteria are present in our case like; hypomelia of both upper and lower limbs (tetra-phocomelia), craniofacial (eyes and nose abnormalities), facial hemangioma, hydrocephaly, cleft palate, short neck, sacral agenesis, the heart also impacted, renal anomalies with cryptorchidism and a low number of platelets [21-23]. In our patient, we could not point precisely to the low platelet number either due to the pathology itself or the giant liver hemangioma despite the mass regressing during the follow-up period. Unfortunately, the family denied the genetic counselling despite their instructions about the certain complex chromosomal abnormalities which are distinguishing features of this syndrome (autosomal recessive trait), which means both parents need to have the abnormal gene for a child to have it (the Mendelian conditions would be given a high risk) [23-25]. There is not a current cure for phocomelia, however, our team; of pediatric surgeons, paediatricians, pediatric cardiologists, gastroenterologists, neurosurgeons, urologists, orthopaedicians, and pediatric psychiatrists try to assign and recommend a treatment plan for any abnormalities encountered in this patient by implementing; Surgery, Prosthetics, Physical therapy, Occupational therapy and, Speech therapy. All we understand, caring for a disabled child can be traumatic for some people; the cornerstone in managing both cases is to provide family counselling services when parents generally carry a feeling of blame and responsibility for their children’s deformities. Such conditions often lead to marital and financial problems for the parents, and their appearance needs to be considered an event that permanently alters family life. In our case series, both babies have severely hypoplastic extremities, and the parents should work with the management team to have an experience and help understand how to meet the unique needs of their children.

Conclusion

LDS and phocomelia are diverse in their epidemiology, aetiology, and anatomy. Usually, they require a low threshold and careful intervention to improve functional and aesthetic outcomes. Physicians and caregiver should assign their workup precisely for the examinations following initial diagnosis, prevention of primary manifestations, and prevention of secondary complications. To help manage this condition, a medical professional should conduct a physical examination of the internal organs to rule out any abnormalities or address any as quickly as possible. Pediatric health care professionals should consider genetic counselling to provide families with information on the nature, mode of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions with a discussion about the importance of prenatal and preimplantation genetic testing before pregnancy.

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Conflict of Interest

The authors declare that they have no competing interests. This work is original and has not been submitted to other publishers.

Ethics Statement

Written informed consents were obtained from the patients’ parents who participated and managed in this report for publication and any accompanying images. The study conformed to the guidelines of the institutional review board of our Institution, which approved its ethical aspects.

Authors Contributions

All authors were involved in the conception, design, literature search, drafting and approval of the manuscript.

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