

Bilateral Symmetrical Distal Lower Limbs Phocomelia, Micrognathia/Retrognathia, Cleft Palate and Other Congenital Anomalies

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Abstract

Phocomelia is an extremely rare congenital disorder characterized by aplasia or hypoplasia of the long tubular bones with more or less intact hands and feet. It is known in both autosomal recessive and sporadic forms, showed a marked increase in incidence in the 1960s due to the toxicological effects of thalidomide drug. Certain syndromes are reported to be associated with phocomelia. Micrognathia, retrognathia and cleft palate are craniofacial birth defects which appear as isolated phenotype or as part of syndromes. A full-term, newborn male presented with phocomelia, micrognathia/retrognathia, cleft palate and other congenital anomalies have been investigated.

Keywords: Phocomelia; Micrognathia; Retrognathia; Cleft palate; Thalidomide

Introduction

Phocomelia (seal limb) is an extremely rare congenital disorder that characteristically affects the limbs [1]. It can affect either the upper limbs, lower limbs or both [2]. It is characterized by aplasia or hypoplasia of the long tubular bones with more or less intact hands and feet [3]. Bone missing may be proximal (humerus or femur), distal (radius and ulna or tibia and fibula) or complete, with the upper portion of the limb being most severely affected [2-4]. In extreme cases, the hands or fingers are attached directly to the shoulder and the most proximal elements (those closest to the shoulder) are entirely missing [4]. Although various factors can cause phocomelia, the prominent roots came from the drug use of thalidomide, which had been prescribed as mild sedative in the early 1960, and from genetic inheritance [1-7].

Phocomelia is transmitted as an autosomal recessive trait with variable expressivity and malformation is linked to chromosome 8 [8]. Certain syndromes are reported where phocomelia is one of the features along with other congenital malformations i.e. Roberts syndrome, Schizel Phocomelia syndrome, DK Phocomelia syndrome Odontotrichomelic tetramelic ectodermal dysplasia, congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome and Syndrome of spleno-gonadal fusion [4,9-13].

Epidemiologic data on phocomelia are scarce. A total of 141 phocomelia cases are registered gave an overall total prevalence of 0.62 per 100,000 births [4].

Craniofacial anomalies are very common birth defects and can appear as isolated phenotype or as part of syndromes [14]. Cleft lip and palate is one of the most common birth defects with the highest prevalence of 1 in 500 live births [15,16]. Micrognathia (unusually small mandible) occurs as an isolated form or as part of syndromes [17,18]. It has been reported that all patients with micrognathia are also affected with retrognathia (abnormal posterior positioning of the mandible or maxilla relative to the facial structure) due to the small size and the growth pattern [18].

Treatment of patients with such conditions is aimed to improve quality of life. Surgery for cleft lip and/or palate and correction of limb abnormalities may be indicated. Speech assessment and special education are required. Periodic follow up of psychomotor development and physical growth is needed. Follow-up assessment of speech development and hearing if cleft lip and palate are present; and screening for developmental delays or learning disorders; monitoring for specific ophthalmologic, cardiac or renal anomalies are included in the management protocols. Genetic counseling has been indicated. Carrier testing for at-risk family members is possible if the pathogenic variants have been identified in the family [19-21].

OPEN ACCESS

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Received Date: 09 May 2018

Accepted Date: 18 Jun 2018

Published Date: 22 Jun 2018

Citation: Mousa Tia KI, Al Ghafri AA. Bilateral Symmetrical Distal Lower Limbs Phocomelia, Micrognathia/Retrognathia, Cleft Palate and Other Congenital Anomalies. *J Clin Case Rep.* 2018; 1(1): 1009.

ISSN 2643-8194

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Case Presentation

A full term, breech-assisted delivered, new-born (38 week gestation) male baby; small for gestational age, is presented. Birth weight is 2.1 kg. Apgar score is 5 at 1 minute, and 9 at 5 minutes. The baby developed tachypnea shortly after birth and was shifted immediately to Special Care Baby Unit (SCBU) where oxygen via head box was started and peripheral capillary oxygen saturation (SPO₂) was maintained. Clinical examination showed dysmorphic features, mild low set ears, short neck, moderate to severe micrognathia/retrognathia and cleft palate. There was bilateral symmetrical dysplastic lower limb, absent marks of knees, absent tibia and fibula, rocker-bottom feet and talipes equinovarus. The upper limbs are normal. The chest is clear. The cardiovascular examination reveals normal 1st and 2nd heart sounds and faint systolic murmur (grade 1-2/6) at the left parasternal border; there are no signs of heart failure. Blood pressure is normal. Abdomen is soft and lax; no organomegaly. Central nervous system examination reveals a conscious and active baby without an obvious neurological deficit. The mother is 46 years old G16P15 with history of one baby early neonatal early death. Antenatal and perinatal history was uneventful. Complete blood count, renal function test, liver function test, serum electrolytes and bone profile all are normal. An infantogram (figure 1) demonstrates small, retrotopic lower jaw (retromicrognathia) and bilateral symmetrical missing tibia and fibula (distal phocomelia). The feet are attached directly to the thighs. A 2-dimensional echocardiography demonstrates a small patent ductus arteriosus with right to left shunt. Abdomen and cranial ultrasounds are normal. ISCN karyotype normal male (46, XY).

Discussion

Phocomelia in the complete form, the arm and forearm are absent in the upper limb and the thigh and leg are absent in the lower limb (the hands and feet sprout directly from the trunk). The deficiency may be proximal (arms and thighs missing) or distal (forearms and legs missing). This malformation was seen with thalidomide embryopathy or could be a part of some pseudo-thalidomide syndromes, which could be familial.

Conditions and syndromes reported with phocomelia and/or craniofacial abnormalities include the following:

Sporadic phocomelia

Is a very rare genetic disorder inherited as autosomal recessive trait or as the result of spontaneous mutations. In such cases, there is 25% chance for a child to be affected, provided both parents are carriers. Thus, there is significantly increased risk for phocomelia when parents have consanguinity. However, without the ability to obtain a reliable family history, the presence of hereditary phocomelia cannot be determined [22].

Thalidomide-induced phocomelia

This drug became over-the-counter in 1960, and shortly thereafter, 5,000 to 7,000 infants were born with signs of phocomelia. Other abnormalities included eye deformities, blindness, deafness, and abnormalities of the cardiac, gastrointestinal, genitourinary, and nervous systems. The drug was withdrawn from western markets in 1962. After 1965, the drug was remarketed in several countries for the treatment of erythema nodosum leprosum [22].

Roberts syndrome (RBS)

Is characterized by prenatal growth retardation (ranging from



Figure 1: An infantogram of the full term baby demonstrates small, retrotopic lower jaw (retromicrognathia) and bilateral symmetrical missing tibia and fibula (distal phocomelia). The feet are attached directly to the thighs.

mild to severe), craniofacial findings (including microcephaly and cleft lip and/or palate) and limb malformations (including bilateral symmetric tetraphocomelia or hypomelia caused by mesomelic shortening). Upper limbs are more severely affected than lower limbs. Other limb malformations include oligodactyly with thumb aplasia or hypoplasia, syndactyly, clinodactyly and elbow and knee flexion contractures. Craniofacial abnormalities include cleft lip and/or cleft palate, premaxillary prominence, micrognathia, microbrachycephaly, malar flattening, down slanted palpebral fissures, widely spaced eyes, exophthalmos resulting from shallow orbits, corneal clouding, underdeveloped ala nasi, beaked nose, and ear malformations. Intellectual disability is reported in the majority of affected individuals. Mortality is high among severely affected pregnancies and newborns. Mildly affected individuals may survive to adulthood [20,21].

Schinzel phocomelia syndrome: is characterized by limb/pelvis hypoplasia/aplasia

Specifically, intercalary limb deficiencies and absent or hypoplastic pelvic bones. The phenotype is similar to that described in a related multiple malformation syndrome known as Al-Awadi/Raas-Rothschild syndrome. The additional important feature of large parietooccipital skull defects without meningocele, encephalocele or other brain malformation has thus far been reported only in children with Schinzel phocomelia syndrome [23].

DK Phocomelia (von Voss-Cherstvoy) syndrome

Is a rare autosomal recessive inherited syndrome, associated with phocomelia, oligodactyly, thrombocytopenia and heart, brain and kidney malformations [24,25].

Odontotrichomelic tetramelic ectodermal dysplasia

Is an ectodermal dysplasia affecting the hair, teeth and nails with malformation of all four extremities including absence of several rays in hands and feet [11].

Child syndrome

(Congenital hemidysplasia with ichthyosiform erythroderma and limb defects) is a rare disorder characterized by birth defects of several organs and systems, including the skin, viscera, musculoskeletal system and central nervous system. Different patients reported

with half-sided osteochondrodermatitis, nevus ichthyosiformis, hemidysplasia, ichthyosiform erythroderma, limb defects, progressive bilateral optic nerve atrophy and congenital heart disease [26-29].

Syndrome of spleno-gonadal fusion

Is a rare polytopic condition of abnormal fusion between the spleen and the gonad or remnant of the mesonephros. It has been associated with other congenital anomalies including limb defect, micrognathia, cardiac defect, cleft palate, spina bifida, facial muscle agenesis and malformation of the anus [30].

Treacher collins syndrome (Mandibulofacial dysostosis)

Is a condition that affects the development of bones and other tissues of the face. The most affected people have micrognathia, cleft palate, eye abnormalities and hearing loss. Mandibulofacial dysostosis with microcephaly syndrome shares some overlapping features with Treacher Collins syndrome [31].

Goldenhar-Gorlin syndrome

Manifests a number of craniofacial abnormalities that usually involve the face (hemifacial microsomia/micrognathia), eyes (epibulbar dermoid) and ears (microtia). It may also be associated with varying degrees of systemic and vertebral malformations [32,33].

Nager acrodysostosis

Is a rare syndrome characterized by malar hypoplasia, micrognathia, cleft palate, no eyelashes, eyelid coloboma, small or unusually formed ears and conductive hearing loss. Upper limb anomalies include absent thumbs and syndactyly and partial or complete absence of the radius. Lower limbs abnormalities also noted. Less commonly, affected individuals have abnormalities of the heart, kidneys, genitalia, and urinary tract. Most cases are sporadic, but autosomal recessive inheritance has been suggested [34].

Pierre robin syndrome

(Also known as Pierre Robin sequence, Pierre Robin malformation, Pierre Robin anomaly or Pierre Robin anomalad) is a congenital condition of facial abnormalities characterized by cleft palate, micrognathia, retrognathia and glossoptosis. Pierre Robin sequence may be caused by genetic anomalies at chromosomes 2 [35].

Trisomy 13 and 18

The major phenotypic features of trisomy 13 are small for gestational age fetuses, with central nervous system anomalies, midline facial defects and urogenital malformations. Facial anomalies typical for trisomy 13 are mainly midline cleft lip/palate, arhinia, cyclopia and proboscis [36]. Trisomy 18 phenotype typically shows facial dysmorphism with micrognathia, low set abnormal ears, hirsutism together with multiple organ system malformations such as spina bifida, omphalocele, heart defects, clubfeet and radial aplasia [36].

The case described in this report had bilateral, symmetrical lower limb phocomelia, micrognathia, retrognathia, cleft palate, talpis equinovarus and patent ductus arteriosus with right to left shunt. No other abnormality detected at this level. The described malformations makes this case a rare one and academically important. The final diagnosis in this patient is not reached as the genetic workup is not completed. However, among the syndromes described above, the most plausible diagnostic consideration is Roberts syndrome.

Conclusion

Sonographic prenatal anomaly scan is advised for all pregnant

women at risk, as most of the anomalies can be detected if the scan is performed at around 18-20 weeks of gestation.

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