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Case Report

Lethal Neonatal Rhizomelic Dwarfism: A Report of Two Cases

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ABSTRACT

Rhizomelia is a condition in which there is a shortness of proximal limbs, while dwarfism connotes a short stature. Both rhizomelia and dwarfism are uncommon diseases of the newborn, while concurrence of both diseases in the newborn is rarer. We report two cases in which both diseases occurred concurrently and both had a lethal outcome. The first case had the characteristic phenotypic features of thanatophoric dysplasia type I, while the second case had characteristic physical and radiological features of Osteogenesis imperfecta type II. The challenges of diagnosis and treatment are highlighted with a view to proffering solutions that may positively influence management of children with similar clinical features in future.

Key words: Rhizomelia, Lethal neonatal rhizomelic dwarfism, skeletal dysplasia.

INTRODUCTION

Skeletal dysplasias are a heterogenous group of bone growth disorders in which the skeleton is abnormally developed, thereby resulting in abnormal shape and size of the skeleton. Presentation at birth is associated with different foetal outcomes. [1] Short limb dwarfism is part of tubular bone chondrodysplasia syndromes. It can manifest in both lethal and non lethal forms. Thanatophoric dysplasia type I (TDI) and osteogenesis imperfect (OI) type II, are some of the lethal forms. [2]

Thanatophoric dysplasia (TD) is the most common lethal osteochondrodysplasia with a prevalence of 1:20,000 to 1:40,000 live births. [3] Males are affected more than females. It is characterized by markedly underdeveloped skeleton and short limb dwarfism. Thanatophoric dysplasia is caused by activation of the Fibroblast Growth Factor Receptor 3 gene (FGFR3) located on the short arm of chromosome 4 leading to negative regulation of bone growth. [4,5]

There are two clinical types of TD which closely resemble each other in their clinical features. Type 1 is more common and has the amino acid arginine, at 248 position substituted by cysteine. Type II has the lysine at 650 position replaced by Glutamate in most cases. [6,7] The phenotypic features of Type I, include a normal-shaped skull and curved long bones, especially seen in femur bone, whereas type

II is associated with a clover leaf-shaped skull and straight femur. [3-5] Other phenotypic features of both types include severe shortening of limbs, macrocephaly with prominent forehead, wide fontanelles, prominent eyes, long narrow bell shaped thorax resulting in pulmonary hypoplasia. [7] Radiological features are short, cupped and anteriorly splayed ribs with severe hypoplasia of pelvic bones, short and flared femur with medial spike. [8]

Osteogenesis imperfecta is a group of rare inherited disorders of connective tissue with the common features of excessive fragility of bones and osteopenia. [9] It is caused by mutations in the collagen, type I, alpha1 and collagen type I, alpha 2 genes, which encode the alpha 1 and the alpha 2 chain of type I procollagen, respectively. [9] Molecular genetic studies have detected more than 150 mutations of these genes. [9] These mutatons reduce the amount of collagen type I produced by the organism leading to bone fragility.

The incidence is 1:20,000 and occurs in all races and ethnicity. [10] It is mostly inherited as an autosomal dominant disorder, but autosomal recessive forms have been reported. [10,11] The clinical classification by Silence et al is the most helpful in prognosis and genetic counseling; and it groups OI into four types: Type I, II, III and IV which are mild, perinatally lethal, progressively deforming and moderately severe respectively. [11] Osteogenesis imperfecta is characterized by multiple and recurrent fractures, which can occur in utero or peripartum or postpartum period. Other features include blue sclera, otosclerosis with hearing loss, high arched palate, hyperlaxity of ligaments and skin, defective dentition, scoliosis and growth retardation.

Prenatal ultrasonographic examination is an excellent method for early detection of skeletal dysplasias and fractures in utero, [12,13] However technical difficulties in performing the ultrasound such as poor foetal position, oligohydramnios, multiple gestations, maternal obesity or late gestational age at examination may delay or prevent an accurate diagnosis. [14,15] Prenatal diagnosis can also be made by chorionic villus sampling and analysis of collagen synthesis by foetal cells between 10 and 12 weeks of gestation. [16,17] There is no cure for OI and the management is multidisciplinary. [18]

CASE REPORTS

Case I

A female baby was born at 35 weeks gestational age by cesarean section at LAUTECH Teaching Hospital, Ogbomoso. Indications for cesarean section were a previous scar, polyhydramnios and recurrent severe respiratory distress in the mother. The mother was a 33-year-old gravida 2, para 1 Nigerian woman in a non-consanguineous marriage with normal antenatal clinic booking parameters. There was no family history of any congenital anomaly and she had no history of drug, alcohol, or tobacco abuse in antenatal period. There was no exposure to teratogenic agents. She was admitted two times for threatened abortion at gestational ages of 18 weeks and 26 weeks.

Ultrasonographic evaluations done at the point of a threatened abortion revealed a singleton having a significant difference in disproportionate foetal parts with shortened femur length and normal other foetal parameters. Another ultrasound examination done at the gestational age of 29 weeks showed polyhydramnios and shortening of both femoral and humeral lengths. The femora showed proximal focal deficiency and were also curved in shape. A sonographic diagnosis of rhizomelic dwarfism had been made at 18 weeks gestational age.

Despite the potential lethal outcome, the parents decided to continue the pregnancy. Mother also refused to give her consent for further confirmatory diagnostic procedures such as amniocentesis for cytochemistry. She later developed recurrent episodes of respiratory distress which was adduced to the splinting of the diaphragm by the polyhydramnios) at

31weeks of gestation. She was subsequently admitted at the hospital at 32 weeks gestation, following this, she requested that her pregnancy be terminated.

A Consultant Paediatrician was present at the delivery to resuscitate the high risk newborn. At birth the baby did not initiate spontaneous breathing. The general appearance was that of a female infant with generalized cyanosis. Active resuscitation was immediately commenced with clearing of the airways, tactile stimulation, intermittent positive pressure ventilation (IPPV) by Ambu bagging connected to oxygen. An endotracheal tube was passed and manual ventilation continued. Oxygen saturation was 45%. The Apgar score was 2 at 1 and 5 minutes. Umbilical catheter was passed and the baby commenced on IV 10% Dextrose in water at 60mls/kg body weight/24 hrs.

Despite active cardiopulmonary resuscitation, the baby could not sustain spontaneous respiration. The condition of the baby gradually worsened until she developed cardiorespiratory arrest that could not be reversed. Child was certified dead 55 minutes after delivery.

The baby had dysmorphic features: large head, wide fontanelles, sutural diastasis, prominent forehead, depressed nasal bridge, prominent eyes, short neck, small, narrow chest, protuberant abdomen bilaterally symmetrical, short upper and lower limbs with excess skin folds, short fingers, bowed (curved) thighs held in abduction and external rotation (fig.1). She had normal female external genitalia and patent vaginal and anal orifices. The birth weight was 2.9 kg (>50th percentile), head circumference 38.0 cm (> 90th percentile); crown to heel length 39.5cm (<10th percentile); trunk length 20.7 cm (within normal range); chest circumference 27.0 cm (<50th percentile), abdominal circumference 33.5 cm.

The parents refused postmortem radiograph and autopsy examination studies on the baby and thereafter the parents took away the body.

Fig.1: Newborn female with dysmorphic features.

Case 2

A 29 hours old female neonate presented at Our Lady of Apostle Catholic Hospital (OLACH) Oluyoro, Ibadan, Oyo State, Nigeria on account of a worsening breathlessness which was first noticed shortly after birth. Ten hours after delivery pain was noticed in both upper and lower limbs. There was excessive crying whenever the mother touched the limbs and fever.

The mother of the baby girl was a 35-year old Nigerian, gravida 2, para 1. She registered for the antenatal care of this index pregnancy at the Oyo State Maternity Hospital, Yemetu, Ibadan at 6 months gestational age. There was no significant maternal illness throughout the pregnancy period. The mother used only the routine antenatal drugs during the pregnancy. There was no family history of tendency to fractures and no family history of any baby with fracture at birth.

Three prenatal ultrasonographic examinations were done at about 25 weeks, 34weeks and 37 weeks gestational ages. The ultrasound scan at 34 weeks showed abnormally short femoral lengths of 3.6 cm each (Normal range 6.6-7.0 cm). The mother was informed about the foetal

abnormalities detected and advised to see her Obstetrician for further counselling. The counseling was done by only the Obstetrician as there was no post screening result multidisciplinary counseling team. Mother however, unilaterally decided on her own to go for the third ultrasound scan three weeks after the second one. The third ultrasound scan revealed that the baby was in a breech position and again confirmed the foetal micromelia (femur length 3.9 cm). The mother had premature prolonged rupture of membranes 3 days before the delivery at 40 weeks gestation. There was no history of peripartum fever.

The onset of labour was spontaneous and the labour lasted for about 7 hours. The baby was delivered by assisted breech at a Primary Health Centre (PHC). Other health services had been paralyzed by industrial action/strike at the Government hospital (a secondary health care centre) where the mother had antenatal care. The baby cried weakly immediately after birth. Baby's Apgar score and birth weight were not recorded. Difficulty in breathing was noticed within a few hours after delivery and got progressively worse. The respiratory rate also increased. Subsequently, the baby was referred to OLACH on the second day after birth for further management.

The child was admitted into the out-born section of the Special Care Baby Unit (SCBU) of OLACH. On examination the baby was found to be critically ill, in acute respiratory distress, flaring of alae nasi, respiratory rate of 80/minute, marked subcostal and lower sternal retractions, and intense cyanosis, severe hypoxaemia (SPO_2 62%). She had one episode of generalized seizure which was controlled by intravenous phenobarbitone therapy. She had blue-gray sclera, low set ears and high arched palate. Musculoskeletal system examination revealed short and deformed extremities, with the deformities worse in the right upper and lower limbs; subcutaneous crepitus of the right humerus, ulna and fibula, right femur, patellar region; lower third of tibia and fibula bilaterally. The skull was soft and had sutural diastasis. The posterior fontanelle was widely patent.

The admission weight was 2.5 kg, head circumference of 33.5cm, chest circumference 29. 0 cm, crown to heel length 34.0 cm (< 5^{th} percentile), trunk length 15.5 cm. The baby was febrile with a skin (axillary) temperature of 39ºC.

A diagnosis of OI type II with severe perinatal asphyxia and neonatal sepsis was made. Radiographs revealed generalized osteopaenia of the mineralized bones. The humerus, radius and ulna, femur and tibia and fibula were shortened, deformed and showed multiple healing fractures (fig. 2).

Basic life support measures were instituted, including maintenance of patent airways, oxygen therapy through nasal prongs, monitoring of arterial oxygen saturation by pulse oximetry, Intravenous line was established for fluid and drug therapy. Septic screening was performed, including full blood count (FBC). Lumbar puncture for cerebrospinal fluid (CSF) analysis was deferred because the patient was too sick for the procedure. Blood sugar (glucose) was monitored. Blood culture, serum electrolytes, urea and creatinine could not be done due to financial constraint as patients pay out of pocket for medical services in the hospital.

The full blood count at age 2 days showed PCV 47%, WBC 14,100/mm^3, Neutrophils 60%, Lymphocytes 30%, Eosinophils 1%, Monocytes 3%; Blood film for malaria parasites was negative. The baby was on nil per oris (NPO) initially for 4 days and thereafter fed by orogastric tube with expressed breast milk. Sepsis was treated with IV Ceftazidime and Metronidazole for 10 days. The baby however, developed anaemia with PCV of 32% on the 15^{th} day after admission. The anaemia was corrected with whole blood transfusion.

The parents had financial constraints and could not keep up with the increasing requests to pay for review by an orthopedic surgeon, and continuance of admission and management. Consequently, they requested

for the baby to be discharged and baby was eventually discharged against medical advice (DAMA) on the 19th day of admission when there was still evidence of hypoxaemia by pulse oximetry. The parents did not keep their follow-up appointment as agreed before leaving the hospital and baby was reported to have died at home 5 days after DAMA at a postnatal age of 24 days.

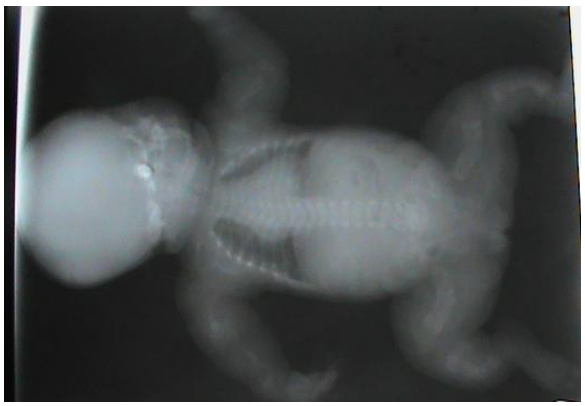

Fig.2: Radiographs showing generalized osteopaenia of the mineralized bones.

DISCUSSION

The management of babies presenting with severe disease conditions in the neonatal period can be challenging, most especially in resource constrained settings. [1-2] Thus, it was not unexpected that the outcome of the two reported neonates was fatal. The odds that the disease conditions would result in death even in developed communities were quite high. [2,5] The term 'thanatophoric' derived from the Greek word "thanatophorus'' meaning ''death bringing'' was first used by Maroteaux and Lamy in 1967. [4] Type II Osteogenesis imperfecta is perinatally lethal, while type IV OI has a severe presentation which could result to death. [11]

The financial constraints on the part of the parents of the patient with phenotypic and radiological features of osteogenesis imperfect hindered our ability to confirm and to determine the type. Similarly postmortem examinations were not conducted on both neonates for different reasons. Inability to investigate and document information on these rare diseases is a hindrance to generation of information and development of research. It is a missed opportunity to fill in missing gaps in knowledge.

Improvement in the management of both cases could have been achieved by a much more proactive management on the part of the managing physicians. [18-19] In a much more ideal situation both mothers would have had the opportunity to discuss with the paediatricians ante-natally about the chances and the health status of their babies post-delivery. This could probably have helped the mothers of the babies with thanatophoric dysplasia or Osteogenesis imperfect to reach an informed decision on the termination of their pregnancies or deliveries much earlier.

Modern day management requires a patient centered approach to managing patients with disease conditions. [20] It was quite clear that the mother whose baby had Osteogenesis imperfecta was not given the option of deciding whether she wanted active resuscitation or not for her newborn infant. Parents have a right to these decisions when their babies have defects or diseases not compatible with life.

In conclusion, the lack of equality in access to health care in the cases reported can be addressed by the provision of an affordable National health insurance scheme which is accessible to all. The rich individuals in the society can also assist in delivering health care to the public or society by taking care of the less privileged ones through philanthropy or through funding government, society or individual health projects and making them available to the society at free or subsidized costs. The public needs to be better educated about cooperation with health workers by agreeing to run necessary investigations with particular emphasis on post mortem examination in order to fill the gaps in knowledge. On a final note, health providers need to shift from a physician centered approach to patient centered approach.

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