CASE REPORT

Grebe Syndrome: A Rare Association with Congenital Heart Disease

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ABSTRACT

Grebe syndrome is a very rare form of short-limbed dwarfism. It is a genetic condition, passed by autosomal recessive inheritance. It is characterized by marked acromesomelic shortening of all the four limbs. There are no other associated anomalies. The affected baby has normal intelligence and normal life span. We present here a case of Grebe syndrome along with congenital heart disease.

Key words: *Grebe syndrome. Short limb dwarfism. Acromesomelic shortening. Congenital heart disease. Septal defect.*

INTRODUCTION

Grebe described this entity for the first time in 1952.[1] Grebe syndrome is a distinct type of dwarfism in which all the four limbs have marked acromesomelic form of shortening associated with normal head and trunk. The severity of anomalies progresses distally along the limbs, so that the fingers and toes lose their phalangeal appearance and become mere knobs.[2] This disorder is inherited as an autosomal recessive trait.[3] Except for the limb deformities, rest of the body systems are normal. Mental and physical development is also normal.

We present a case of 3 months old boy who presented with typical clinical and radiological features of Grebe syndrome. On diagnostic work up, he was also found to have congenital heart disease in the form of atrial and ventricular septal defects. This association has not been reported earlier.

CASE REPORT

A 3 months old male baby presented to the Paediatric Outpatient Department of Combined Military Hospital, Rawalpindi with complaints of multiple congenital anomalies involving all the four limbs. There was no history of any other problems. He was the first baby of consanguineous parents, delivered spontaneously at term with no perinatal complications. Pregnancy was reportedly un-eventful. Mother took haematinics and multivitamins irregularly throughout the pregnancy but there was no history of any other drug intake. There was no history of abortions, miscarriages or death of any siblings or any congenital anomalies or malformations in the family. The baby was on formula feed and being vaccinated.

On examination (Figure 1), he was a healthy looking active baby with marked shortening of all the four limbs. There was no facial dysmorphyism. His fronto-occipital circumference was appropriate for his age. The limb shortening was of acromesomelic type. The forearms were markedly short as compared to the upper arms. The hands were rudimentary and bud like. Both hands had 5 fingers each which were short and appeared like toes. All the digits had complete syndactyly. Both lower limbs also showed severe shortening of acromesomelic type. The feet were also rudimentary and bud like, and had valgus positioning bilaterally. Each foot had 5 rounded and stub like toes (Figure 1). Examination of the heart revealed a grade III pansystolic murmur which was

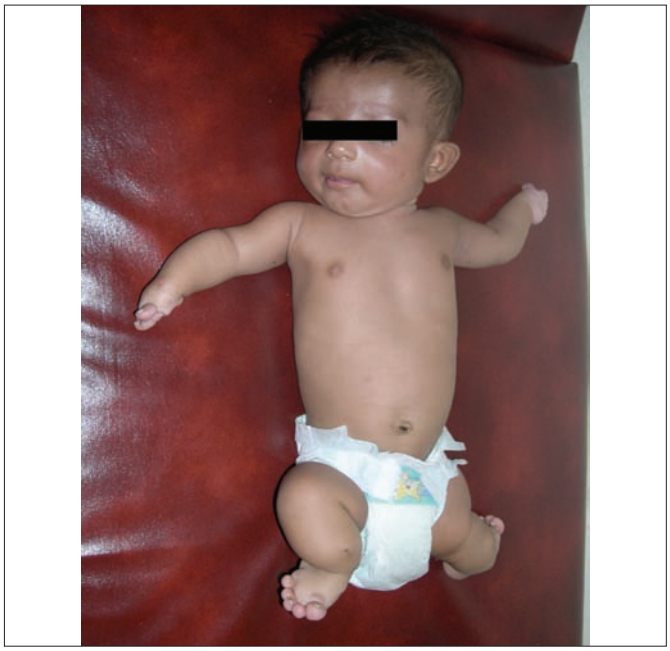

Figure 1: Picture shows a 3 month old baby showing marked acromesomelic shortening of all the four limbs, rudimentary hands and feet, stub like fingers and toes with normal head and trunk.

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best heard at the left sternal edge. Examination of the chest and abdomen revealed no abnormality. Spine and genitalia were normal. X-rays (Figure 2) of upper limbs revealed short, bowed and deformed radii/ulnae as compared to relatively normal humeri. The right hand showed complete agenesis of carpal and metacarpal bones and phalanges. Left hand also showed complete agenesis of carpal and metacarpal bones, however, phalanges of ring and little finger were present along with a hypoplastic distal phalanx of the thumb. Both lower limbs had shortened and deformed tibiae, bilaterally absent fibulae and relatively normal looking femora. Right foot showed hypoplastic calcaneum and medial three metatarsal bones. Left foot showed hypoplastic calcaneum with phalanges of big toe only (Figure 2). Echocardiography of the heart revealed an atrial septal defect and a small peri-membranous and mid muscular ventricular septal defect (Figure 3).

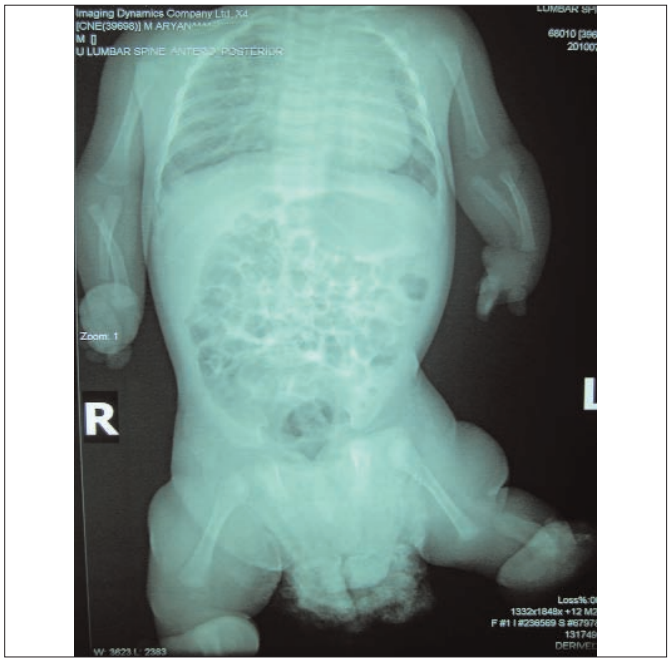

Figure 2: Complete body radiograph shows a normal axial skeleton and rib cage, relatively normal humeri and femora, marked shortening of radii/ulnae and tibiae with absence of fibulae bilaterally. There is almost complete agenesis of hands and feet bones except for few rudimentary phalanges.

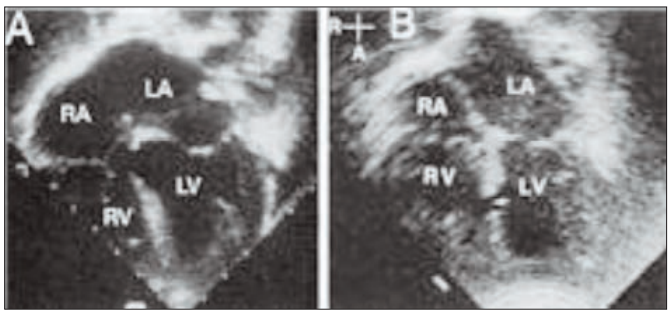

Figure 3: Situs solitus AV and VA concordance small ASD secundum. Perimembranous VSD additional midmuscular VSD moderate elevation of PA pressures aortic arch normal. Good LV function. No LV or RV clot/vegetation.

DISCUSSION

This rare syndrome was first described by Grebe in 1952.[1] Quelce-Salgado reported 47 cases in 5 kindred in an inbred Brazilian population.[4] The largest cluster of people with Grebe syndrome is in Brazil. This patient belonged to the district Chakwal in Northren Punjab province of Pakistan. This rare condition has autosomal inheritance.[3] However, the data suggests that gene has some defect on heterozygotes.[5] Evaluation of both the parents revealed no abnormality. Mutations in the cartilage derived morphogenetic protein 1 (CDMP 1) gene on chromosome 20q11.22 cause Grebe type chondro-dysplasia.[6] This baby was the first born of consanguineous parents. Kulkarni *et al.* have reported the antenatal diagnosis of a case of Grebe syndrome[7], but in this patient it was not suspected antenatally and only came to light after delivery. There was no family history of this or any other congenital malformations.

Clinically, Grebe syndrome is a distinct type short limb dwarfism in which all the four limbs are markedly short as compared to normal head and trunk size. Shortening of limbs is acromesomelic in form. The severity of anomalies progresses distally along the limbs, so that the fingers and toes lose their phalangeal appearance and become mere knobs.[2] In this patient the limbs were markedly short in acromesomelic fashion. The hands were rudimentary and bud like with short 5 fingers each.

Radiologically, it is characterized by a normal axial skeleton and severely shortened and deformed limbs, with a proximo-distal gradient of severity. The humeri and femora are relatively normal, the radii/ulnae and tibiae/fibulae are short and deformed, carpal and tarsal bones are fused, and several metacarpal and metatarsal bones are absent. The proximal and middle phalanges of the fingers and toes are invariably absent, while the distal phalanges are present.[8] In this patient upper limbs revealed short, bowed and deformed radii/ulnae as compared to relatively normal humeri. The hands showed complete agenesis of carpal and metacarpal bones and variable phalanges. Postaxial polydactyly is found in several affected individuals.[7] This patient had normal number of digits but there was syndactyly among all of them. Several joints of the carpus, tarsus, hand, and foot were absent. Heterozygotes presented with a variety of skeletal manifestations including poly-dactyly, brachydactyly, hallux valgus, and metatarsus adductus.

This 3 months old male baby presented with all the clinical and radiological features of Grebe syndrome including marked limb shortening with progressive severity distally along with a normal trunk and axial skeleton. All these features have been reported in medical literature. What makes this case unique is the fact that this baby had associated congenital heart disease which has not been reported previously in a case of Grebe syndrome.

REFERENCES

1. Grebe H. Die achondrogenesis: Ein einfach rezessives Erbmerkmal. *Folia Hered Pathol* 1952; **2**:23.
2. Kumar D, Curtis D, Blank CE. Grebe chondrodysplasia and brachydactyly in a family. *Clin Genet* 1984; **25**:68-72.
3. Grada-Castro JM, Perez-Comas A. Non-lethal achondrogenesis in two Puerto Rican sibships. *J Pediatr* 1975; **87**:948-52.
4. Qualce-Salgado A. A new type of dwarfism with various bone aplasia and hypoplasias of the extremeties. *Acta Genet Stat Med* 1964; **14**:63-6.
5. Quelce-Salgado A. A rare genetic syndrome. *Lancet* 1968; **1**: 1430.
6. Basit S, Naqvi SK, Wasif N, Ali G, Ansar M, Ahmed W. A novel insertion mutation in the cartilage-derived morphogenetic protein-1 (CDMP 1) gene underlies Grebe type chondrodysplasia in a consanguineous Pakistani family. *BMC Med Genet* 2008; **9**:102.
7. Kulkarni ML, Kulkarni BM, Nasser A. Antenatal diagnosis of Grebe syndrome in a twin pregnancy by ultrasound. *Indian Pediatr* 1995; **23**:1007-11.
8. Costa T, Ramsby G, Cassia F, Peters KR, Soares J, Correa J, *et al.* Grebe syndrome: clinical and radiographic findings in affected individuals and heterozygous carriers. *Am J Med Genet* 1998; **75**:523-9.