Grebe Syndrome - Case Report With Review of Literature

Rashmi N[1] and Kiran HS[2]

[1]Department of Paediatrics, JSS Medical College, JSSAHER, Mysore, India
[2]Department of Internal medicine, JSS Medical College, JSSAHER, Mysore, India

Correspondence:
Dr. Rashmi N
Associate Professor in Pediatrics
JSS Medical College, JSSAHER
Mysore, Karnataka, India.
Email: dr.rashminagaraj@gmail.com

DOI: 10.3126/jnps.v41i3.31170
Submitted on: 2020-09-12
Accepted on: 2021-11-14

Acknowledgements: None
Funding: Nil
Conflict of Interest: None declared
Permission from IRB: Yes

To cite this article: Rashmi N, Kiran HS. Grebe Syndrome - Case Report With Review of Literature. J Nepal Paediatr Soc. 2021;41(2):447-50.

ABSTRACT

Grebe syndrome is a rare genetic condition characterised by short limb dwarfism. It is transmitted by autosomal mode of inheritance. There are no associated anomalies and the affected child has normal intelligence and normal life span. This syndrome has a very low incidence and needs to be differentiated from other forms of short limb dwarfism since treatment options may vary. We have described here a severely affected case of the same with review of literature.

Key words: Acromesomelic shortening; Chondrodysplasia; Grebe syndrome; Short limb dwarfism

INTRODUCTION

Grebe's chondrodysplasia or Grebe and Quelce-Salgado syndrome or Nonlethal achondrogenesis, first described by Grebe in 1952,1 is a distinct type of dwarfism inherited as an autosomal recessive trait[2,3] and characterized by marked acromesomelic shortening of all the four limbs with normal head and trunk. It is a rare genetic entity, which has been described in about 70 cases till date belonging to 12 families or inbred groups in a Brazilian population.[4] The affected child has normal intelligence and all the other systems are also normal.

CASE REPORT

A six year old boy born to consanguineously married couple presented to our Paediatric outpatient department with history of multiple limb defects since birth. Milestones of development were normal and there was no history of any other problems. He was the first child, delivered spontaneously at term with no perinatal complications. Pregnancy was reportedly uneventful. Mother had taken haematinics and multivitamins irregularly throughout the pregnancy but there was no history of any other drug intake or exposure to radiation or TORCH infections. There was no history of abortions, miscarriages or death of any siblings or any congenital anomalies or malformations in the family. Child was immunised to date and belonged to a lower socio-economic status. On examination, he was a healthy looking active child with severe shortening of all the four limbs. He was short statured (height being < 3rd centile for age and gender on the NCHS charts). There was no facial dysmorphism. His occipito-frontal circumference (51 cm) was appropriate for his age. The limb shortening was of acromesomelic type. The forearms were markedly short as compared to the upper arms. All five fingers of both hands were rudimentary and bud like. Both lower limbs also showed severe shortening of acromesomelic type and were more severely affected than the upper limbs. The feet were also rudimentary with bud like toes, with the left great toe and right little toe being absent. There was bilateral valgus deformity of the feet as also absence of fibula on both sides evidenced by absent lateral malleoli. (Figures 1, 2)

Examination of the chest and abdomen revealed no abnormality. Spine and genitalia were normal. Systemic examination was unremarkable. X-rays (Figure 3) of both lower limbs showed shortened and deformed tibiae, bilaterally absent fibulae and relatively normal looking femora, and deformity of the feet with maldevelopment of digits. However, in the upper limbs, carpal and metacarpal bones were present bilaterally with hypoplastic and altered shapes of phalanges and under developed

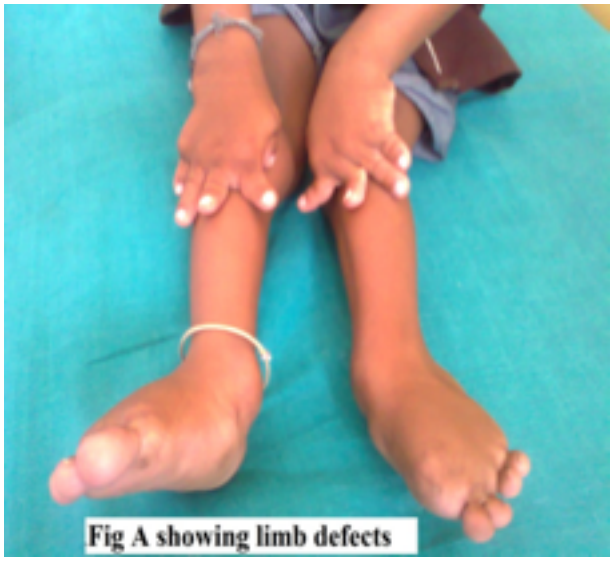

Figure 1. Limb defects

Figure 2. Child with short stature and acromesomelic shortening of limbs

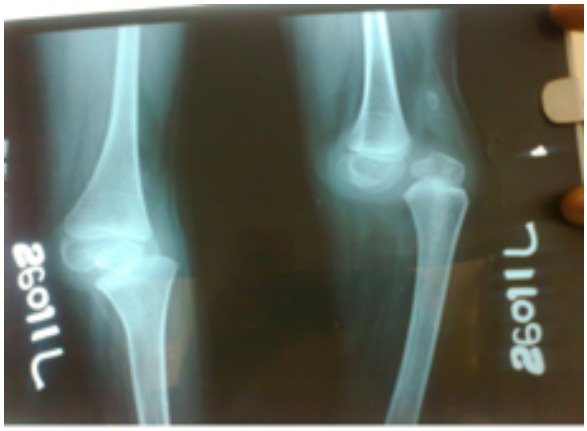

Figure 3. Xray lower limbs depicting bilaterally absent fibulae and deformed tibiae

thumbs with relatively normal looking, but short radii and ulnae.

Examination of his parents did not reveal any abnormality. Studies on molecular genetics were not feasible in our set up. However diagnosis was obvious based on history of consanguinity and classical phenotypic and radiological features.

DISCUSSION

Quelce-Salgado reported 47 cases in five kindred in an inbred Brazilian population. Brazil is known to have the largest cluster of people with Grebe syndrome.[4] It affects both the sexes and is evident from birth. The legs are more severely affected than the arms. The severity of anomalies progresses distally along the limbs, so that the fingers and toes lose their phalangeal appearance and look like just knobs.[2] Postaxial polydactyly occurs in more than half the cases.[3] Except for the limb deformities, rest of the body systems are normal with normal facies and intelligence and normal life span. The mode of inheritance of this rare condition is autosomal recessive[3] and this child was the first born of consanguineously (uncle-neice) married parents.

Radiologically, it is characterized by short and deformed middle long bones, fusion of carpal bones and several metacarpals and metatarsals, and absence of proximal and middle phalanges. The humeri and femora are relatively normal, the radii / ulnae and tibiae / fibulae are short and deformed, carpal and tarsal bones are fused, and there is absence of several metacarpal and metatarsal bones. The proximal and middle phalanges of the fingers and toes are invariably absent, while the distal phalanges are present.[3] In our patient, there were short radii and ulnae as compared to relatively normal humeri and absence of fibula on both sides. One more characteristic feature of this condition is absence of vertebral abnormalities.

The diagnosis is mainly made based on the clinical and radiological features. Most of the clinical and radiological findings in the child reported here, including marked limb shortening with progressive distal severity along with normal trunk and axial skeleton and normal intelligence, fit into the diagnosis of acromesomelic dysplasia Grebe type (AMDG). However, mutation analysis of the CDMP1 (cartilage derived morphogenetic protein 1) gene could confirm the diagnosis, which was not done in our set up due to financial constraints.

The less common symptoms described are, unusual oral frenula, missing teeth, cutaneous webs between eyelids, atresia of external ear canal, intercrural pterygium, bifid or absent patella, low acetabular angle, spina bifida occulta, bifid ribs, short sternum, scoliosis, ambiguous external genitalia, penile ectopia, penile torsion, ectopic testes, underdeveloped vagina, underdeveloped uterus, inguinal hernia, and abnormal scalp hair. The rare complications include stillbirth and infant death.[5]

Treatment includes a multidisciplinary approach with orthopedician, prosthetist and occupational therapist and involves use of artificial limb prosthesis both for functional and social reasons. In children with fibular deficiency like in our case, tenoligamentocapsulotomy can be performed and the corrected position maintained in plaster[6].

Grebe syndrome (OMIM 200700) is due to a missense mutation in the gene encoding cartilage-derived morphogenetic protein-1. The protein encoded by the CDMP1 gene is a member of the bone morphogenetic protein (BMP) family and the TGF-beta superfamily[2] and is located on chromosome 20q11.2. The abnormalities reported in heterogygotes are absent phalanges, anatomical changes of the phalanges, talipes equinovarus, polydactyly, and double halluces, brachydactyly, hallux valgus, and metatarsus adductus.[7] Neither of

the parents of our child showed any abnormalities. The absence of the ulna and the phalanges is characteristic of Grebe syndrome.[7,8] Complete expression of the gene for Grebe syndrome results in total failure of bone formation. CDMP1 gene mutations have also been associated with Hunter-Thompson syndrome, Du Pan syndrome and brachydactyly type C, which form the differential diagnoses.[9] However, phenotypes in these syndromes are different from those in Grebe type.[10]

CONCLUSIONS

It is important for both paediatricians and orthopedicians to be aware of this rare condition, so that early referral and appropriate corrective treatment may improve the quality of life of the affected child and the family. Except that this rare syndrome could cause a social stigma, the long term prognosis is good as these individuals can lead an almost independent life in view of normal intelligence, especially if severe deformities are corrected early.

.

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. PMID: 6705242 DOI: 10.1111/j.1399-0004.1984.tb00465.x.
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. Rittler M, Higa S. Grebe syndrome: a second case with extremely severe manifestations. J Med Genet 1997; 34:1038-1039. DOI: 10.1136/jmg.34.12.1038.
6. Shatilov OE, Rozkov AV, Cheminova TV. Reconstructive surgery for fibular deficiency. Prosthet Orthot Int 1991; 15:137-139. DOI: 10.3109/03093649109164649.
7. Quelce-Salgado A. A rare genetic syndrome. Lancet 1968; 1:1430.
8. Kulkarni ML, B Kumar, A Nasser, BM Kulkarni. Grebe syndrome. A very severely affected case. J Med Genet. 1991;32(4): 326-7. DOI: 10.1136/jmg.32.4.326-a.
9. Martinez-Garcia M, Garcia-Canto E, Fenollar-Cortes M, Aytes AP, Trujillo-Tiebas MJ. Characterization of an acromesomelic dysplasia, Grebe type case: novel mutation affecting the recognition motif at the processing site of GDF5. J Bone Miner Metab. 2016 Sep;34(5):599-603. DOI: 10.1007/s00774-015-0693-z.
10. Jessica A. Suarez Z, Ricardo AA, Sebastian RS. Grebe syndrome. Case report. Rev Asoc Argent Ortop Traumatol 2018; 83 (1): 50-53. DOI: http://dx.doi.org/10.15417/677