

Case Report

A case report of recurrent achondroplasia in fetuses of normal parents

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Received: 09 April 2015

Accepted: 07 May 2015

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ABSTRACT

Achondroplasia, a skeletal dysplasia has an incidence of 1 in 15000 to 1 in 30000 live births. It is inherited in an autosomal dominant manner. The occurrence of recurrent achondroplasia in babies born to normal parents is rare. The present case report is one such type. A female fetus of 27 weeks gestational age was brought to the Department of Anatomy, Karpaga Vinayaga Institute of Medical Sciences, Maduranthagam. There was frontal bossing of forehead, rhizomelic type of limb shortening with limitation of elbow extension in the fetus. The mother of the fetus, who is 26 years old, gave history of recurrence of such condition. Her first pregnancy was a twin pregnancy, conceived by natural methods, where one of the twins was a male baby who also had achondroplasia and died 2 hours after delivery. The other twin is a girl and the child has delayed developmental milestones. Her second pregnancy was uneventful. The present fetus under study is from her third pregnancy. Her marriage is of second degree consanguineous type. The age of her husband is 36 years old. Germinal mosaicism has been attributed for the causation of recurrent achondroplasia in children, whose parents are normal. 80% of achondroplasia is due to a new mutation. Only 20% of achondroplasia is inherited. Increased paternal age is a risk factor for new mutations to occur. The other investigations of the case and the genetic analysis are described further in the article.

Keywords: Achondroplasia, Autosomal dominant, Germinal mosaicism, FGFR-3

INTRODUCTION

Achondroplasia is a skeletal dysplasia of autosomal dominant trait with complete penetrance. The incidence of achondroplasia has been reported to be 1 in 10000 to 1 in 30000 births, irrespective of their race and sex.¹ It is the most common type of short limb dwarfism leading to rhizomelic shortening of limbs. Achondroplasia is caused by mutation of fibroblast growth factor receptor-3 gene, located at the short arm of chromosome 4 at locus 16.3.² This anomaly is due to glycine to arginine substitution at codon 380.³

This mutation leads to increased tyrosine kinase activity in the cartilaginous growth plate receptors, thereby inhibiting bone growth.⁴ Bones formed by endochondral

ossification are affected, thereby leaving the skull vault unaffected, which is formed by membranous ossification.⁵

Although achondroplasia is an autosomal dominant condition, only 20% of this condition is inherited. 80% of the condition is sporadic⁶ and occurs due to *de novo* mutation of the FGFR-3 gene in parent's sperm cell or ovum before conception. The incidence of *de novo* mutation of the FGFR-3 gene increases with the paternal age, known as paternal age effect, as the mutation occurs mostly in the male germ line.⁷

Paternal age over 35 years has been strongly correlated with new mutations occurring in achondroplasia and other autosomal dominant disorders.⁸ 97% of *de novo* achondroplasia are caused by a transition mutation

(c.1138G.A) associated with the p.gly380arg amino acid change in the protein's transmembrane domain.⁵

The recurrence of *de novo* achondroplasia in children born to normal parents is rare, with an incidence of less than 1%.⁹ The recurrence of children affected by achondroplasia, born to normal parents indicates the risk of germline mosaicism.¹⁰

The present report is about one such case, where there is a recurrence of achondroplasia in fetuses of normal parents.

CASE REPORT

A female fetus of 27 weeks gestational age was brought to the Department of Anatomy of our institution. On observation, the fetus had shortening of all limbs, with prominent forehead and varus deformity. No other defects were visible on inspection. On further examination, there was limitation of bilateral elbow extension in the fetus. The placenta and umbilical cord was normal (Figure 1).



Figure 1: 27 weeks female fetus showing shortening of limbs.

The examination of the fetus was done after obtaining written consent from the parents. The age of the mother is 26 years and that of the father is 36 years. It is a second degree consanguineous marriage. The mother of the fetus gave a history of recurrence of achondroplasia. Her first pregnancy was twin pregnancy, conceived by natural methods. One of the twins was a male child, who had achondroplasia and died two hours after delivery. The other twin is a female child, with delayed developmental milestones. Her second pregnancy was uneventful and

she delivered a normal male baby. The present fetus under study is from her third pregnancy.

The radiological examination of the fetus showed a large calvarium with frontal bossing, shortening of long bones, increased radiolucency of femur, small flattened pelvic bones with narrow sacroiliac notches (Figure 2A, 2B).



Figure 2A: Radiograph showing shortening of long bones in fetus.



Figure 2B: Radiograph showing shortened right lower limb bones.

The second trimester ultrasound evaluation of the fetus has showed the femur length less than fifth centile with altered femur to foot ratio (<1). The Biparietal diameter, abdominal circumference and chest circumference were within normal limits (Figure 3). The diagnosis of achondroplasia was made.



Figure 3: 2-D ultrasound picture showing shortening of lower limb.

DISCUSSION

Achondroplasia is an autosomal dominant trait with complete penetrance, which denotes even one mutant allele of the FGFR3 gene, is sufficient to result in disease in an offspring. Homozygous achondroplasia results, when two mutant achondroplasia alleles are inherited, one from each parent by the offspring. Homozygous achondroplasia children have severe phenotype with small thoracic cage, leading to respiratory distress, brainstem compression, neurological deficits etc. Most of these children die within first year of life.¹¹

Mutations in the fibroblast growth factor receptor-3 gene have been attributed to result in achondroplasia. Two mutations in the FGFR3 gene (c.1138G>A and c.1138G>C) have been noted to result in achondroplasia. Both mutations lead to same alteration in the FGFR3 gene, leading on to replacement of glycine amino acid with arginine amino acid at protein position 380. The c.1138G>A transition in FGFR3 is more commonly reported in de novo cases of achondroplasia than the c.1138G>C transversion.³ Our present case is de novo achondroplasia in a fetus, with history of recurrence in sibling, born to same normal parents.

Recurrence of sporadic achondroplasia in siblings, born to normal parents is a rare entity. Paternal age effect on mutation in sporadic cases of achondroplasia was noted by Penrose (1955). Analyses of birth incidence of achondroplasia have shown that, unaffected fathers in their fifties are 10 fold more likely to have offspring with a *de novo* achondroplasia mutation when compared with unaffected fathers in their twenties.¹²

The pathophysiology of genetic mutation in *de novo* achondroplasia remains hypothetical. Germline mosaicism has been suggested by Fryns et al.¹³ for the case of three siblings affected by achondroplasia, born to normal parents. This theory is attractive, but one would expect such recurrences for other fully penetrant mutations. Hence Optiz¹⁴ in his review has suggested the theory of unstable premutation with reduced penetrance or phenotrance to explain both the phenomenon. The chance occurrence of repetitive independent mutations is another theory proposed for recurrence of *de novo* mutations resulting in achondroplasia, which is although not very common.

About 80-90% of achondroplasia is caused by *de novo* mutations and all these *de novo* mutations studied so far were found to have occurred on paternal chromosomes.¹⁵ This gender bias is due to difference in germ cell biology of male and female lineages. Spermatogonium undergoes mitotic divisions before meiotic divisions that lead to the formation of sperms. Some of the products of the mitotic divisions are reserved to replenish the supply of spermatogonia.¹⁶ Mutations occurring during DNA replication can therefore accumulate, providing a basis for paternal age effect and for germinal mosaicism.

In this present case, the recurrence of *de novo* achondroplasia could be due to germline mosaicism or unstable premutation with reduced penetrance. The couple has two live children, one female child from first pregnancy who has delayed developmental milestones and one male child from second pregnancy. The male child is normal. If the hypothesis of germline mosaicism is considered, then the chance of the children getting affected by achondroplasia is unlikely, whereas if the unstable premutation theory is considered, the risk of achondroplasia is high. The unaffected father was not willing for sperm donation and hence the hypothesis of germline mosaicism could not be substantiated.

Second trimester ultrasonography to detect congenital anomalies has to be emphasized to all sectors of people around the world.¹⁷ Prenatal genetic diagnosis can be made through procedures like amniocentesis and chorionic villus sampling. The fetal achondroplasia parameters can be evaluated by 2-D ultrasonography. One of the most important determinations that should be made in skeletal dysplasia by ultrasound is neonatal or infantile lethality. A proper diagnosis is necessary to do appropriate counselling.

Life expectancy in heterozygous achondroplasia is normal in majority of the people. Complications of achondroplasia are disability in arm function and locomotion, thoracolumbar kyphosis, spinal canal stenosis, recurrent otitis media, obesity, respiratory complications, jaw malocclusion, craniocervical stenosis, medullary compression (narrow foramen magnum), upper spinal cord compression etc.

The effective management of complications due to achondroplasia can be done, to provide a near normal life expectancy to the affected people. Human growth hormone has been used to increase the stature, but it is no longer recommended.¹⁸ Surgical interventions like enlargement of foramen magnum, in case of severe stenosis, lengthening of limb bones, tibial osteotomies, lumbar laminectomy etc. are being done to manage the complications of achondroplasia.

Recent therapeutic strategies involve utilisation of some chemical agents or receptor blocking antibodies that would downregulate the excessive tyrosine kinase activity of the receptors.¹⁹ Molecular therapy involving C-type natriuretic peptide, to downregulate the fibroblast growth factor induced activation of mitogen-activated protein kinase signalling pathways, in growth plate chondrocytes is used to counteract the effects of the achondroplasia mutation in mice. This therapy is suggested as a possible treatment for achondroplasia in humans.²⁰

The recent therapeutic strategies are in the initial phase. In developing countries, where gene therapy is not affordable, a proper counselling to the parents about the problem, steps to be taken to avoid recurrences and alternative methods for having a healthy baby should be emphasized.

CONCLUSION

The need for prenatal genetic diagnosis is increasing in the present scenario. Although achondroplasia is well recognised at birth due to various interventions like ultrasound findings, prenatal genetic testing etc., there are cases which remain unrecognised at birth. This happens especially in under developed and developing countries, where people do not undergo routine antenatal check-ups. Therefore proper health education and counselling to parents, basic antenatal check-ups and procedures etc., must be emphasized to prevent recurrences of conditions like achondroplasia.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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DOI: 10.18203/2320-6012.ijrms20150184

Cite this article as: Anbumani TL, Anthony Ammal S, Thamarai Selvi A. A case report of recurrent achondroplasia in fetuses of normal parents. *Int J Res Med Sci* 2015;3:1533-7.