

Case Report: Achondroplasia

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Vol. 15, No. 2 (2011-07 - 2011-12)

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Abstract

A boy presented with rhizomelic shortening of limbs and progressive enlargement of head, his skeletal survey showed characteristic phenotypic features of achondroplasia. Achondroplasia has been considered as the most common short-limbed dwarfism syndrome, but there are a variety of other syndromes within this category, and other types of limb shortening, which should be differentiated. There is abnormal physical growth, defective metaphyseal modeling and shortness of tubular bone. Diagnosis is by physical examination, radiographic documentation, and, in some cases, genetic testing.

Key words: Achondroplasia, Disproportionate short stature, Hypochondroplasia
Revised May 21 2011

Introduction

Achondroplasia, a non-lethal form of chondrodysplasia, is the most common form of skeletal dysplasia characterized by short limb dwarfism, affecting the growth of tubular bones, spine and skull. Prevalence is estimated to be 1 in 15000. It is inherited as autosomal dominant trait with complete penetrance. Approximately 80% of cases are due to de novo dominant mutations with a mutation rate estimated to be 0.000014 per gamete per generation[1]. It occurs as a result of mutations in one copy of the fibroblast growth factor receptor 3 gene (FGFR3), of which more than 97% of patients have the same point mutation in FGFR3. The mutation, which causes an increase in FGFR3 function, affects many tissues, most strikingly the cartilaginous growth plate in the growing skeleton, leading to a variety of manifestations and complications[2].

Characteristic phenotypic features include disproportionate short stature, megalencephaly, a prominent forehead (frontal bossing), midface hypoplasia, rhizomelic shortening of the arms and legs, a normal trunk length, prominent lumbar lordosis, genu varum, and a trident hand configuration [3]. We report a case of achondroplasia with its typical features.

Case Report

A 4 months old boy was brought to pediatric department with chief complains of shortening of limbs and progressive enlargement of head, since Clinical examination revealed height of less than 3rd percentile and head circumference more than 97th percentile. Craniofacially the head appeared large with frontal bossing, wide open anterior fontanelle with midfacial hypoplasia, depressed nasal bridge and short neck with redundant skin folds. There was thoracolumbar gibbus and both upper and lower limbs showing rhizomelic pattern of shortening. A mongolian spot was present in lumbosacral region. Motor system examination showed mild hypotonia, flabby muscles with increased range of movements and hyperextension of knee joints and reduced muscle power (3/5) in all four limbs. Milestones were delayed. Radiographs of all bones were taken and they showed characteristic features of achondroplasia. Skull was large with relatively small skull base [Fig 1]. Vertebral bodies were short, flattened with relatively large intervertebral disc space and there was narrowing of spinal canal in lumbosacral region [Fig 2,3]. Iliac wings were small and squared, with horizontal acetabular roof [fig 4]. Limb bones were short with metaphyseal cupping and flaring, with irregular growth plates [fig 3]. Hands were broad with short metacarpals and phalanges with trident configuration. All tubular bones were short except fibula [Fig 5].



Figure 1. Radiograph of skull shows enlarged skull with relatively small skull base birth. He was born full term without uneventful gestation period without any birth injuries. The parents were of normal height, healthy and non-consanguineous. Family history was negative for heritable diseases such as meta-bolic disorders or other neurological diseases. No other family members were known to have similar phenotype.



Figure 2. Lateral radiograph of vertebral col-umn short vertebral bodies with relatively large IVD space.



Figure 3. Radiograph showing narrowing of spinal column in lumbo-sacral region and short tubular bones with irregular growth plates and cupping and metaphyseal flaring.

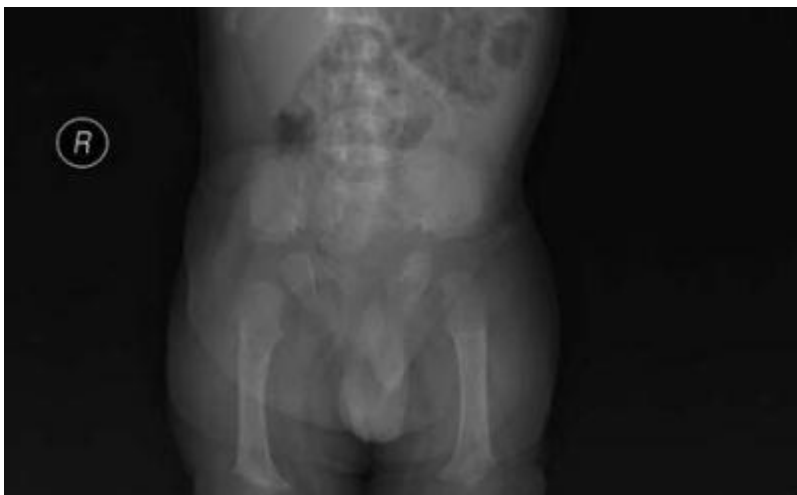


Figure 4. Radiograph of pelvic bones showing small and squared iliac wings with horizontal acetabular roofs.

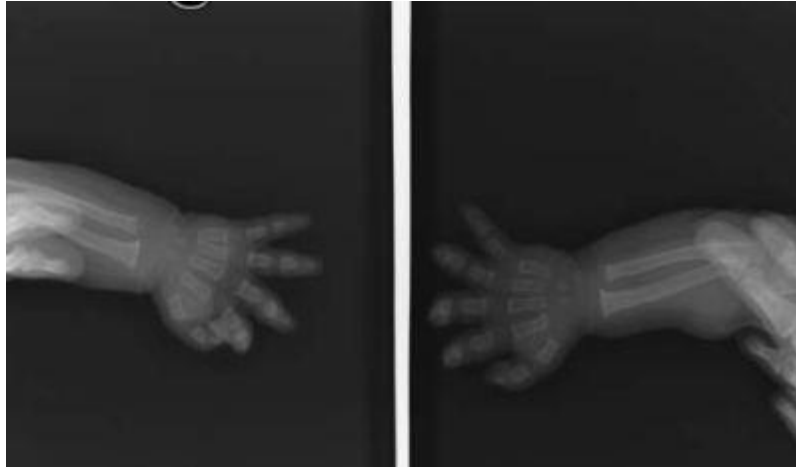


Figure 5. Radiograph of hand showing short metacarpal and phalanges with trident hand configuration.

Discussion

Achondroplasia is the most common form of skeletal dysplasia, affecting growth of tubular bones, spine and skull. Achondroplasia is an autosomal dominant disorder with complete penetration. The gene of Achondroplasia was localized to 4p16.3[4,5]. Subsequently mutation of fibroblast growth factor receptor 3(FGFR3) gene within the region 4p16.3 was reported as cause of Achondroplasia[6]. In heterozygous state Achondroplasia is nonlethal with normal life span and normal intelligence. However they are at risk like cervicomedullary compression, spinal stenosis, obesity, obstructive sleep problem[7,8]. In homozygous state Achondroplasia is a lethal condition. When both parents are heterozygous with Achondroplasia, there is 25% risk of homozygous Achondroplasia in their offspring.

All patients with typical achondroplasia have mutations at FGFR3 codon 380 [1]. In the FGFR3 mutation group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. The mutation maps to the transmembrane domain of the receptor is thought to stabilize receptor dimers that enhance receptor signals, the consequences of which inhibit linear bone growth[6,9]. Achondroplasia behaves as an autosomal dominant trait and most cases arise from a new mutation to normal parents. Such couples have a 50% risk of transmitting their condition, heterozygous achondroplasia to each offspring, as well as a 25% risk for homozygous achondroplasia. The latter condition exhibits intermediate severity between thanatophoric dysplasia and heterozygous achondroplasia[9,10]. Disorders involving transmembrane receptors result from heterozygous mutations of genes encoding these receptors: FGFR3 and PTHR. The mutations cause the receptors to become activated in the absence of physiologic ligands which accentuates normal receptor function of negatively regulating bone growth. The mutations act by gain of negative function [9]. Recurrent mutation G-to-A transition at 1138 nucleotide position of transmembrane domain of FGFR3 gene account for majority of the cases and G-to-C transversion at same position is responsible for the remaining cases. However, rare mutations involving other codons of transmembrane domain and other region of FGFR3 gene have also been described in patients with achondroplasia phenotype[10,11,12].

Characteristics clinical features are typically present at birth with short limbs, a long narrow trunk, and a large head with midfacial hypoplasia and prominent forehead. The limb shortening is greatest in the proximal segments (rhizomelic limb shortening) and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus and Lumbar lordosis are often found. Progressive narrowing of interpedicular distance between L1-L5, smaller greater sciatic notch, short tubular bone, square shape iliacs, contracted base skull and long fibula. Usually, birth length is slightly less than normal but occasionally plots within the low-normal range [13,14].

Skeletal radiographs confirm the diagnosis. The calvarial bones are large, whereas the cranial base and facial bones are small. The vertebral pedicles are short throughout the spine as noted on a lateral radiograph. The interpedicular distance, which normally increases from the first to the fifth lumbar vertebrae, decreases in achondroplasia. The iliac bones are short and round, and the acetabular roofs are flat. The tubular bones are short with mildly irregular and flared metaphyses. The fibula is disproportionately long compared with the tibia. Intelligence is normal unless central nervous system complications develop[15]

Clinical diagnosis is definite based on physical features (present even at birth).The couples can be counselled regarding risk of recurrence based on whether they are affected or unaffected. Mutational analysis become necessary to provide prenatal diagnosis in both high risk and low risk pregnancy. In addition positive mutation gives added proof for the diagnosis and avoid mislabeling of disease.

Prenatal diagnosis of homozygous Achondroplasia can be made by mutation detection at 10-12 week of gestation as against 16-20 week by ultrasonographic examination. Ultrasonographic examination can detect shortening of long bones only in late pregnancy (third trimester)[16]. Prenatal diagnosis can be provided early in pregnancy by DNA based methods on chorionic villi [2,16,17].

Risk of recurrence in family with sporadic cases is estimated to be 1 in 443[6]. This is said to be due to mosaicism in one of the parents. If one of the parent is affected with Achondroplasia the risk to offspring of recurrence is 50% for either sex .If both parents are affected then 25% children will be normal, 50% heterozygous and 25% will be homozygous mutation. Homozygous Achondroplasia is always lethal[6,12,16].

References

1. Bellu AG, Heffron WT, Horton WA . Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am J Hum Genet 1995; 56:368-373.
2. Chitayat D, Fernandez B, Gardener A. Compound heterozygosity for the achondroplasia-hypochondroplasia FGFR3 mutations: prenatal diagnosis and post-natal outcome. Am j med genet 1999; 84:401-405.
3. Cohen MM. Some achondroplasia with short limbs molecular perspectives. Am j med genet 2002; 112:304-313.
4. Francomano CA,Ortiz de luna RI, Hefferon TW: Localization of the achondroplasia gene to the distal 2.5 mb of human chromosome 4q. Hum molec genet: 1994 May; 3(5):787-92.
5. Le MM, Rousseau F: A gene for achondroplasia-hypochondroplasia maps to chromosome 4q. Nature genet 1994; 6: 318.
6. Shiang R, Thompson LM, Zhu YH, Church DM. Mutation in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism achondroplasia. Cell 1994; 78: 335-342.
7. Health supervision for children with achondroplasia. American academy of pediatrics of committee on genetics. Pediatrics 1995, 95: 443-445.
8. Pauli RM, Horton VK, Glinski LP, Reiser CA. Prospective assessment of risks for cervicomedullary-junction compression in infants with achondroplasia. Am J Hum Genet 1995; 56: 732-744.
9. Patil SJ, Banerjee M. Mutation analysis in Indian children with achondroplasia-utility of molecular diagnosis. Ind J Pediatr 2008,76: 147.
10. Vazo Z, Francomano CA. The molecular and genetic basis of FGFR3 disorders,the achondroplasia family of skeletal dysplasia. Endocrine reviews 2000; 21 (1):23-39.
11. Camera G, Baldi M, Striscicuglio P. Occurrence of thanatophoric dysplasia type 1(R248C) and hypochondroplasia(N540K) mutation in to patients with achondroplasia phenotype. Am VJ Med Genet 2001; 104: 277-281.
12. Ikegawa S, Fukushima Y, Isomura M, Takada F: Mutation of FGFR3 gene in one familial and six sporadic cases of achondroplasia in Japanese patients. Hum genet 1995 ; 96 :309-311.
13. Spranger JW, Brill PW, Poznanski AK. Bone Dysplasias: An Atlas of Genetic Disorders of. Skeletal Development, 2 nd ed. Oxford, England: Oxford University Press; 2002: 336-338.
14. kaissi AA, Klausfer K. Progressive and limitations as first alarming sign in a boy with a case of short limb dwarfism. Cases Journal 2008; 1: 63: 125-129.
15. Oberklaid F, Danks DM, Jensen F, Stace L, Rosshandler S. Achondroplasia and hypochondroplasia. Comments on frequency, mutation rate, and radiological features in skull and spine. J Med Genet 1979; 16: 140-46.
16. Modoff P, Horton K, Paul RM. Error in the prenatal diagnosis of children with achondroplasia. Prenat Diagn ,1996; 16: 525-530.
17. Gooding HC, Boehm K, Thompson RE. Issues surrounding prenatal genetic testing for achondroplasia. Prenatal diagnosis 2002; 22: 933-940.
18. Mettler G, Fraser CF, Recurrence risk for sibs of children with "sporadic" achondroplasia. Am J Med Genet 2000; 90:250-251.

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Curr Pediatr Res 2011 Volume 15 Issue 2