

Case report:

OROFACIAL MANIFESTATIONS OF ACHONDROPLASIA

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ABSTRACT

Achondroplasia (Online Mendelian Inheritance in Man [OMIM] 100800), is considered as a form of skeletal dysplasia dwarfism that manifests with stunted stature and disproportionate limb shortening. Achondroplasia is of special interest in the field of dentistry because of its characteristic craniofacial features which include relative macrocephaly, depressed nasal bridge and maxillary hypoplasia. Presence of large head, implanted shunt, airway obstruction and difficulty in head control requires special precautions during dental management. The current case report highlights the orofacial manifestations of Achondroplasia in a young pediatric patient, along with the multidisciplinary treatment (including the dental treatment) done for the patient which also might help the general practitioners in better understanding of the condition.

Keywords: Achondroplasia, craniofacial manifestations, short stature, mutation

INTRODUCTION

Achondroplasia also known as *Chondrodysplasia fetalis* is a non-lethal form of chondrodysplasia. It is transmitted as an autosomal dominant trait with complete penetrance (Jones, 1988; Gorlin et al., 1990). It has a prevalence estimated to be 1 in 15000-40000 cases worldwide. Approximately 80 % of cases are due to de novo dominant mutations with a mutation rate estimated to be 0.000014 per gamete per generation. It occurs as a result of mutation in one copy of the fibroblast growth factor receptor 3 genes (FGFR3) ([OMIM] for gene 134934) of which more than 97 % of patients have the same point mutation in FGFR3. The common mutation causes a gain of function of the FGFR3 gene, resulting in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix

production leading to a variety of manifestations and complications. The gene has been mapped to band 4p16.3.

General physical features include a disproportionate short stature, lordotic lumbar spine, a trident hand configuration, limitation of elbow extension, rhizomelic shortening of the arms and legs, prominent buttocks and a protuberant abdomen. The radiological features include small cuboid vertebral bodies with progressive narrowing of the caudal interpedicular distance, lumbar lordosis, and thoracolumbar kyphosis with occasional anterior beaking of the first and second lumbar vertebrae, small iliac wings with a narrow greater sciatic notch and short tubular bones with metaphyseal flare and cupping (Langer et al., 1967).

Craniofacial features include enlarged calvarium with hydrocephaly, brachycephaly, midfacial hypoplasia, low nasal bridge,

prominent forehead and dental malocclusions.

The condition should be well differentiated from hypochondroplasia, thanatophoric dysplasia, non-syndromic craniosynostosis and Crouzon's disease with acanthosis nigricans.

CASE REPORT

A twelve year old Indian male patient, born to non-consanguineous parents in Baltimore, Maryland, U.S.A, reported to the Department of Oral Medicine and Radiology with a chief complaint of bad breath from mouth since past one month. The ante-natal history of the patient revealed that the patient was a result of G2P0A1, spontaneously conceived after three years of marriage (G1 was aborted at two months of gestation, although the cause was not known). No history of fever, rashes, joint pain, lymphadenopathy, hypertension, diabetes mellitus or medications (other than hematenics) was given by the patient's mother. The natal and post-natal history revealed that the patient was delivered by caesarian section and at eight and half months of gestation, probably because of cephalo-pelvic disproportion. The patient had a large and dysmorphic head at the time of birth. Post natal physiological events were in normal range. Medical history revealed that the patient was a known case of achondroplasia.

Anthropometry (at age 12) revealed a height of 124 cm (10th percentile= 139.5 cm), weight of 32 kg, mesomelic dwarfism with upper limb to lower limb ratio of >1 (expected ≤1) and an arm span of 100 cm (expected to be 124 cm). The gross motor developmental milestones were delayed significantly which might be due to the large head but fine motor developmental milestones, social and adaptive milestones and language milestones were found to be normal at a 12 year old level. Patient gave a history of profuse sweating. Currently, the patient was on calcium and vitamin D supplements.

The patient appeared to be well adjusted, healthy and intelligent. General physical examination showed short stature, rhizomelic shortening of the arms and legs (Figure 1) and a trident hand configuration. Extraoral examination revealed facial features such as brachycephaly, midfacial hypoplasia, flat nasal bridge, frontal bossing and competent lips. A concave facial profile was also noticed, however, the mandible appeared normal and the chin was not prominent (Figure 2). Intraoral examination revealed permanent dentition. The size, number and form of teeth were normal with Class I Molar relationship on both sides with mild anterior open bite and spacings in mandibular teeth. The periodontium was found to be healthy.

The plain computed tomogram (CT) of the brain that was performed at the age of one and half years showed moderate degree of hydrocephalus. The lateral cephalogram revealed brachycephaly and mid facial hypoplasia. The maxillary incisors were proclined relative to the Frankfort horizontal plane and the mandibular incisor angulations were normal relative to the mandibular plane. The panoramic radiograph showed complete set of permanent dentition including third molars with normal development and spacings in mandibular anterior teeth. The postero-anterior cephalogram revealed enlarged calvarium with increased transverse diameter. The hand wrist radiograph revealed trident hand configuration and according to the Fish's skeletal maturity index, the patient was in stage 3 (Figure 3) and was in the pre-pubertal stage. Radiograph of lower limb antero-posterior (AP) view revealed shortening and increased apparent thickness of the femur, tibia and fibula bilaterally with flaring of the acetabula. Also, there was shortening of the long bones of upper extremities, proximal more than distal. The thoracic and lumbar vertebrae showed decreased AP diameter of the vertebral bodies, with increased apparent thickness of the discs.

Based on the history, clinical examination and radiological investigations, a final

diagnosis was arrived at achondroplasia. The patient was thoroughly examined in the departments of orthopedics, oral and maxillofacial surgery and orthodontics. The patient's parents were psychologically counseled for the generally good prognosis of the condition. Surgical limb lengthening, reconstructive procedures and orthodontic therapy were planned for the patient. The patient underwent surgical limb lengthening of lower limbs bilaterally as a result of which a gain of height of 8 cm was seen (Figure 4). The patient will be undergoing surgical upper limb lengthening procedure which is planned after three months.

The oral prophylaxis was done for the patient as the oral hygiene of the patient was found to be satisfactory and no periodontal or dental pathology was seen. Presently the dental intervention is being delayed since the patient has to undergo upper limb lengthening. The patient is being motivated for the same and has been kept on regular follow up.



Figure 1: Achondroplastic patient with short stature with rhizomelic shortening of the arms and legs



Figure 2: Lateral view showing concave profile, midfacial hypoplasia, flat nasal bridge and normal appearing mandible



Figure 3: Hand-wrist radiograph showing trident hand configuration and according to the Fish's skeletal maturity index, the patient was in stage 3



Figure 4: Surgical lower limb lengthening

DISCUSSION

Achondroplasia is a non-lethal form of chondrodysplasia which means “without cartilage formation”. Although skeletal dysplasias are relatively rare, it is estimated that 250,000 individuals worldwide have achondroplasia, the most prevalent form of dwarfism (Horton et al., 2007). It is an autosomal dominant disorder whose underlying mechanism is a defect in the maturation of the cartilage growth plate of long bones. Achondroplasia has recently been shown to result from a Gly to Arg substitution in the transmembrane domain of the fibroblast growth factor receptor 3 (FGFR3). By substituting the transmembrane domain of the Neu receptor tyrosine kinase with the transmembrane domains of wild-type and mutant FGFR3, the Arg380 mutation in FGFR3 is shown to activate both the kinase and transforming activities of this chimeric receptor. Residues with side chains capable of participating in hydrogen bond formation, including Glu, Asp, and to a lesser extent, Gln, His and Lys, are able to substitute for the activating Arg380 mutation. The Arg380 point mutation also causes ligand-independent stimulation of the tyrosine kinase activity of FGFR3 itself, and greatly increased constitutive levels of phosphotyrosine on the receptor. As a result, it limits the formation of bone from cartilage (a process called calcification), particularly in long bones. FGFR3 also plays an important role in cell growth and division, determination of cell type, formation of blood vessels, wound healing and embryo development.

In heterozygous state, achondroplasia is non-lethal with normal life span and normal intelligence. However, they are at risk like cervicomedullary compression, spinal stenosis, obesity, obstructive sleep problem. In homozygous state, achondroplasia is a lethal condition in the early few months of life because of severe rib cage deformity that results in respiratory insufficiency. Sobetzko et al. (2000) also reported achondroplasia in a brother and sister with unaffected parents. The sibs shared the classic 1138G-A mutation (134934.0001) and also

shared a 4p haplotype derived from the unaffected father.

Affected babies are short at birth and grow slowly throughout childhood; the average final height for women is 126 cm (4 ft 2 in) and for men is 131 cm (4 ft 4 in). The limbs are relatively shorter than the trunk with the upper arm and the thigh especially shortened. The head is usually large with prominence of the forehead and a flat nasal bridge. The fingers and toes are short and the hands and feet small and wide. Although the majority of affected children will be healthy, approximately 10 % can develop significant complications so routine review by a paediatrician is recommended. A rare complication is cervicomedullary compression (compression of the upper spinal cord at the base of the brain) which can present with episodes of apnoea (stopping breathing). This requires confirmation by a CT or magnetic resonance imaging (MRI) scan and surgical intervention. In the adolescent and adult compression of nerve roots in the spinal canal may occur with the most common symptoms being a sensation of numbness or weakness in the legs.

Dealing with achondroplastic children needs special psychological management during dental treatment, as the presence of disproportionate short stature can cause a number of psychosocial and social problems. Dental development can be delayed in achondroplastic children due to altered bone growth. However, reported no delay in the eruption of the primary and permanent teeth and it was according to the chronological age, which is also consistent with this case. Stafne (1950) reported retarded eruption of many permanent teeth in a 30 year old affected male. Although shunt was reported to be placed in some achondroplastic children due to hydrocephalus (Hunter et al., 1998; Stephen et al., 2005) which makes head control difficult and may necessitate antibiotic prophylaxis before dental treatment (Tong and Rothwell, 2000) but there was no shunt implanted in the presented case. Recurrent middle ear infections are a common problem with a risk of con-

ductive hearing loss. Furthermore, special precautions in head control during dental intervention are essential, due to the possible presence of cranio-cervical instability, foramen magnum stenosis and limited neck extension, as it might result in respiratory complications.

Thus, a patient with achondroplasia not only requires specific medical management but also requires special attention with definitive dental management along with psychological support to help him lead a normal life and cope up with the medical as well as social challenges of life.

ACKNOWLEDGEMENTS

This work was supported by J.G. Leeladhar and J. Lalita (parents). Special thanks to them for their kind support and cooperation.

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