

CASE REPORT

To cite: Rosaline Tina Paul, Biswas P.P., Ligil A.R., Joseph K.Thanikunnel, Hemant Nandan

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J ContempOrthod 2021;5(3): 1-6.

Received on:
12-08-2021

Accepted on:
05-09-2021

Source of Support: Nil

Conflict of Interest: None

Achondroplasia-Differential Diagnosis And Orthodontic implications- A Case Report

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ABSTRACT

Achondroplasia is a common skeletal dysplasia that results in marked short stature. Encountering patients who are medically, physically and genetically challenged in our orthodontic clinical practice is a very common occurrence. A successful orthodontist should handle such patients with great clinical care and tailor his treatment according to the needs of the patient. Here is a case presentation in which a 15 year old girl having Achondroplasia came to our clinic with a chief complaint of inability to clean the teeth properly because of its irregular placement. After receiving the consent of the physician treating the patient, routine blood investigations, chromosomal analysis and routine orthodontic diagnostic tests were performed and fixed appliance therapy was carried out with first four bicuspid extractions. After the treatment the smile and profile improved drastically. Most important aspect was that the time taken for the treatment to complete was just as would be for any other orthodontic patient. The case finished without any untoward complications like resorption or any periodontal problems. In this article, the differential diagnosis and the orthodontic implications of a patient with Achondroplasia is described in detail.

KEYWORDS: Achondroplasia, FGFR3 mutation, Hypochondroplasia, Thanatophoric dystrophy, SADDAN syndrome, Pseudoachondroplasia.

INTRODUCTION

Achondroplasia(Ach) is an autosomal dominant genetic condition and is the most common cause of dwarfism. This term was first employed by Parrot in 1878. It is caused by heterogenous mutation in a gene called Fibroblast Growth Factor Receptor 3(FGFR3)on chromosome 4which codes for FGFR3 proteins. When the FGFR3 proteinsbinds to FG Factors, it slows down the growth of certain bones. In this condition, the affected bone grows disproportionately thereby the growth of the hands and legs are disproportionate to the body length. The incidence of this condition varies from one in 26000 to one in 66000 births.¹ Both heterozygous and homozygous forms occur. The homozygous type is deadly and lethal in the neonatal period of life, whereas the heterozygous type is usually autosomal dominant having 100% penetrance, affecting both males and females equally.

Recent investigations have proved that the expression of this condition was dueto the congenital defect factor receptor FGFR3. To be a lot more specific the recurrent mutation of one aminoalkanoic acid within the transmembrane domain of the FGFR3 macromolecule is the root cause for this autosomal dominant attribute. Moreover, genetic linkage studies confirm that the Ach gene on the short arm of chromosome 4 and mutation analysis prove that an essential amino acid arginine substituted by glycine substitution at residue 380 (p.Gly380Arg) in FGFR3 exists in the majority of the Ach patients in Cauasian, African and Asian population.² Basically FGFR3 signalling affects encompassing bone directly by regulating alternative growth factors signaling pathways in chondrocytes. Inactivation of FGFR3 leads to an increase in expression of (Indian Hedge Hog)IHH, Bone Morphogenic Proteins (BMPs2,4,7), Transforming Growth Factor Beta 1(TgfB1) and Wingless plus int 4(Wnt4), and reduced expression of Noggin, ultimately leading to an

Table 1 Investigations *Blood investigations*

No	Test	Observed value	Units	Biological reference interval
1.	Somatomedin C	328ng/ml	ng/ml	220-972ng/ml for the age of14years
2.	Chromosomal analysis	46,XX normal karyotyping	-	46,XX normal karyotyping
3.	Serum calcium	9.4	Mg/dl	8.8-10.4
4.	Phosphorous	4.7	Mg/dl	2.8-4.8
5.	T 4	9.21	Microgram/dl	5.91-13.2
6.	TSH	2.90	Microliter U/ml	0.51-4.3
7.	Vitamin D1	35	ng/ml	20-50ng/ml
8.	Vitamin D2	35	ng/ml	30-1000ng/ml
9.	Vitamin D3	35	ng/ml	20-50ng/ml

increase in bone mass. The opposite reaction happens on activation of FGFR3 in chondrocytes. The direct result on osteoblasts leads to impaired bone formation. The role of osteoblasts is coupled to osteoclasts throughout bone formation and resorption. Recent studies have indicated that FGFR3 inactivation in osteoclasts impaired bone resorption.³

There are basically four fibroblast growth factor receptors in humans. FGFR3 is one of the four of them. The function of these cell surface receptors is to influence cellular proliferation. FGFR3 is comprised of an extracellular domain (N) with three immunoglobulin-like regions (IgI, IgII and IgIII), a transmembrane domain(TM) and an intracellular tyrosine kinase (TK)⁴(Fig 1)



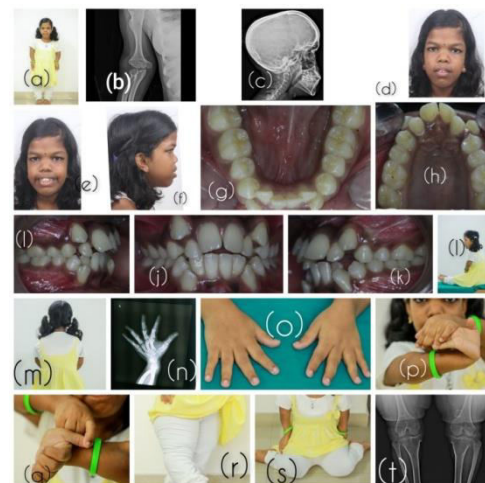
Fig(1):Diagram to explain the structure of FGFR3 .

We can picturize it as an empty cup sitting on the surface of cells, particularly on the surface of chondrocytes which give rise to cartilaginous bone. The common location is in cartilaginous end plate of long bones, calvarial sutures, testes, and the brain. Normally, the FGFR3 is dormant. However, various fibroblast growth factors (FGFs) – mainly, FGFs^{2, 9, 18 and 23} – can act as ligands, binding to the FGF, ultimately effect in filling the cup present on the chondrocytes. This results in demineralization of the receptors, transphosphorylation and trans-activation of tyrosine kinases, and propagation of an intracellular signal. That is, FGFR3 is a negative regulator of chondrocytic bone growth (through shortening of the proliferative phase and accelerating terminal

differentiation). The “full cup”, then, results in a net “slow down” signal inside relevant cells. This condition belongs to something called RAMP disorders – recurrent, autosomal dominant, male biased, paternal age effect disorders – all which probably arise due to their positive selective effect on spermatogonia.⁵

Manifestations of this condition includes short stature, lumbar lordosis, shortening of the arms and legs, short stubby trident hands, outstanding buttocks and a bulging abdomen. Craniofacial malformations are enlarged calvariumsometimes with hydrocephaly and frontal bossing, a depressed nasal bridge, a shortened posterior cranial base, a small foramen magnum, a retrognathic maxilla and an orthognathic mandible. The common orthodontic manifestations could be protrusive incisors, anterior open bite or even severe dental crowding.⁶

Alternative disorders with similar manifestations include Apert syndrome, Noonan syndrome, and multiple endocrine neoplasia type 2B.^{7,8}



(Fig :2a-whole body of the patient,b- rhizomelic disproportion of the limbs,c-pretreatment lateral cephalogram,d,e,f- Pretreatment extraoral,g,h,i,j,k- Pretreatment intraoral,l- lumbar lordosis,m-

kyphosis, n- handwrist radiograph, o- trident configuration, p- hypermobile wrist, q- hypermobile thumb, r, s- hypermobile knees, t- bowing of legs).

CASE REPORT

A 14 year old girl (Fig 2a), who had attained puberty one month ago, with small stature (height of 148.2 cm and weight of 65 kg), short limbs displaying rhizomelic disproportion (Fig 2b), reported with a chief complaint of inability to properly brush and maintain proper oral hygiene due to the irregularities in position of her teeth.

History reveals that at birth she was very much normal, but after 45 days of birth, she had difficulty in suckling breast milk due to the underdeveloped nasal bone and midface in general. This concern leads the parents to seek medical help and the condition was diagnosed after clinical evaluation as Achondroplasia by the general physician

The calvarium exhibited macrocephaly, with frontal and parietal bossing (Fig 2c). A midfacial retrusion and a flat nasal bridge along with a short nasal spine and anteversion of the nose was present (Fig 2d,e,f). She had a small chest, lumbar hyperlordosis, thoracolumbar kyphosis, (Fig 2l,m) short fingers and trident configuration of the hands (Fig 2n,o) and also displayed hypermobility of her wrist and thumb (Fig 2p,q). She also exhibited unusually hypermobile hips (Fig 2r,s) and knees with bowing of the mesial segment of the legs (Fig 2t).

A typical crouch gait accompanied with a decreased forward velocity while walking. Step length and stride length was observed with an increased average forward tilt of the trunk and the pelvis. Additionally, hip flexion and hip adduction while walking was seen in order to balance her body weight.

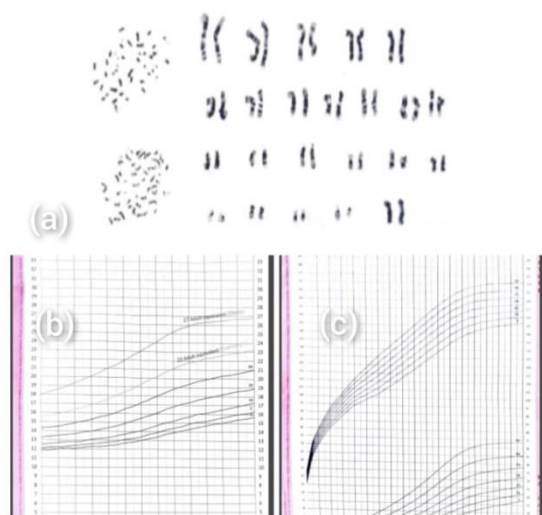


Fig (3): a- chromosomal analysis, b, c- growth analysis chart

The chromosomal analysis report showed a normal karyotype with 46,XX pattern (Fig 3a). The growth chart depicted a short stature and height for her age (Fig 3b,c).

TREATMENT PROGRESS

After ascertaining the consent from the physician treating the patient for Achondroplasia, her first bicusps were extracted and routine fixed appliance therapy was initiated. Segmental arch mechanics for individual canine retraction was performed initially to rule out any untoward side effects in tooth movement. Regular check-ups were performed to verify that no unnecessary events like root resorption occurred. Furthermore, blood and hormonal values were regularly monitored.

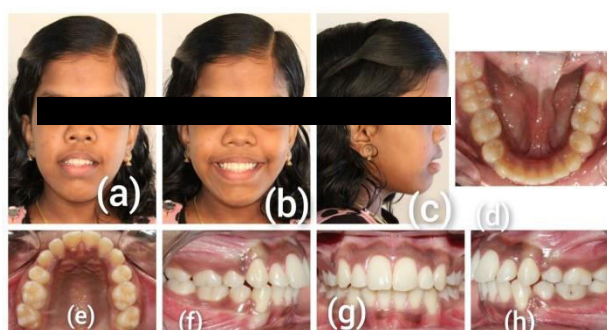


Fig (4) a,b,c –Post treatment extraoral, d,e,f,g,h- post treatment intraoral

Anchorage conservation was satisfactory, but being a high anchorage case, with crowding and proclination space was an issue. The end results were satisfactory both extraorally and intraorally (Fig 4a,b,c,d,e,f,g,h) and the patient appeared to pose a confident smile. Furthermore, in the 7 months post treatment records (Fig 5c,d), nothing abnormal was detected.

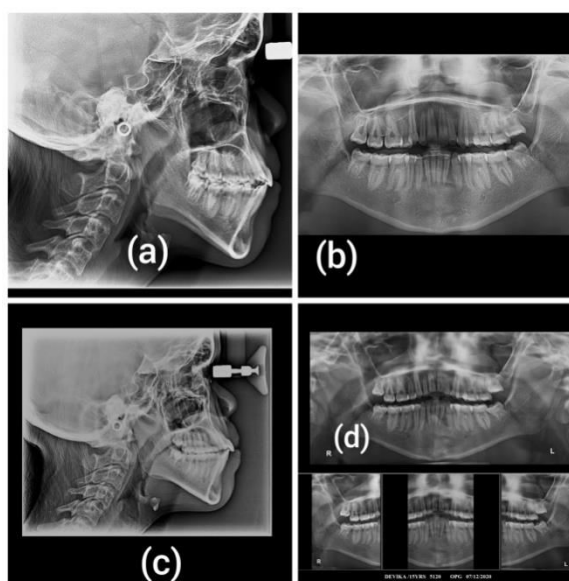


Fig (5):a,b, -post treatment lateral cephalogram and OPG, c,d- 7 It is usually fatal and lethal, sometimes in early infancy.

Table:2 Pre and post cephalometric analysis					
No	Measurement	Average	Observed value		Inference
Skeletal parameters			Pretreatment	Posttreatment	
1.	SNA	82 ⁰ +/-2	78.2 ⁰	78.8 ⁰	Retrognathic maxilla
2.	SNB	80 ⁰ +/-2	78.5 ⁰	78 ⁰	Orthognathic mandible
3.	ANB	3 ⁰ +/-2	-1.3 ⁰	0.8 ⁰	ClassIII skeletal pattern
4.	Mandibular plane	32 ⁰ +/-4	41.7 ⁰	42.6 ⁰	Dolichocephalic
5.	Occlusal plane	14 ⁰ +/-4	25.4 ⁰	29.4 ⁰	Clockwise rotation
Dental parameters					
1.	UI to NA (angle)	22 ⁰ +/-2	47.8 ⁰	33.1 ⁰	Vestibular version
2.	UI to NA (linear)	4 mm	16.5mm	13.7 mm	Protrusion
3.	LI to NB (angle)	25 ⁰ +/-2	46.2 ⁰	26.7 ⁰	Vestibular version become normal
4.	LI to NB (linear)	4 +/-2 mm	8.7 mm	8 mm	Protrusion
5.	Interincisal angle	131 ⁰ +/-6	87.2 ⁰	119.3 ⁰	Protrusion
Soft tissue parameters					
1.	Upper lip to S line	0 mm	6.0 mm	5.2 mm	Protrusive lips
2.	Lower lip to S line	0 mm	6.8 mm	5.2 mm	Protrusive lips

months follow up lateral cephalogram and OPG

DISCUSSION

In general, any short limb dwarfing disorder would fall in the spectrum of the differential diagnosis of Ach. Distinct mutations in FGFR3 could cause variety of allied conditions with shared features and differ principally in severity.⁹ The most common variety being hypochondroplasia that has been recognized as a definite clinical entity for less than around fifty years. This condition is comparatively less frequent and severe than Ach.¹⁰

Hypochondroplasia is a milder version of achondroplasia. There are three specific radiologic features present in Ach but not evident in hypochondroplasia, they are;

- The characteristic proximal femoral bone radiolucency of Ach is never evident in those with hypochondroplasia
- Rhizomelic disparity of the arms, which is uniform in Ach, is absent in hypochondroplasia
- The moderate to marked abnormalities of facial bone contour of Ach is not present in those with hypochondroplasia.

However, molecular testing is mandatory to differentiate hypochondroplasia and Ach.

Thanatophoric dystrophy,^{12,13} was originally identified by Maroteaux et al.¹⁴ Its name implies “death bearing dwarfism”.

It's equally as common as Ach.¹⁵ The clinical and radiographic features resemble Ach, however, it is more severe. There are 2 kinds of thanatophoric dystrophy. Type I has curved, “telephone receiver” femora and extremely flat vertebral bodies, whereas type II has straight femora, taller vertebrae has severe craniosynostosis.^{16,17} Both the types are caused by distinct mutations in FGFR3. It is rare to find any diagnostic confusion between thanatophoric dystrophy and Ach. In SADDAN syndrome,¹⁸⁻²⁰ “SADDAN” stands for “Severe Ach with Developmental Delay and Acanthosis Nigricans”. It uniformly results from a mutation that causes a Lys650Met substitution in FGFR3. Prior to the age at which developmental disturbances could be recognized and before acanthosisnigricans could develop, a molecular evaluation of Ach and SADDAN syndrome is mandatory.

In addition to the FGFR3 family of bone dysplasias, alternative mutations in this same gene could cause Crouzon syndrome with acanthosisnigricans,²¹ Muenke syndrome,²² isolated acanthosisnigricans with or without slow linear growth,²³⁻²⁵ and slow linear growth devoid of unequivocal characters of a bone dysplasia being evident.²⁶ Ach is a metaphyseal dyplastic condition. Other, alternative metaphyseal dysplasias, are the Schmid style of metaphyseal dysplasia²⁷ and cartilage-hair hypoplasia²⁸ distinguished by clinical and radiologic features and age of presentation. Any

rhizomelic dwarfing method would possibly sometimes cause diagnostic confusion.

Pseudoachondroplasia²⁹ deserves special mention. Despite its name it's primarily aspondyloepiphyseal dysplasia with very little features of Ach except rhizomelic dwarfism. It does not have any of the craniofacial characteristics that are seen in Ach. It's usually not diagnosed till the second or third year of life. Radiographs of both the types are dissimilar.

In regards to orthodontic implications, Pauthers,³⁰ Tomoko³¹ and Jennifer³² et al treated Ach patients with multibracketed fixed appliances along with extractions and were able to achieve successful and stable results. They concluded that Ach patients could be treated orthodontically just as any other normal patient.

Celen Pet al even states that they have treated a case with a posterior cross bite uneventfully with a HYRAX rapid palatal expansion device with excellent results. However the author also noted that the treatment of choice was limited in Ach patients, because growth potential was a compromise in such patients.³³

Arlen et al have performed comprehensive surgical correction of severe midfacial skeletal discrepancies in Ach patients using a Lefort I osteotomy procedure. This is a positive indication suggesting no contraindications to surgical procedures in Ach patients.³⁴

CONCLUSION

This case report gives an insight to the orthodontist in the orthodontic treatment of an Ach patient. Most of the clinical features mentioned in literature, such as, retrognathic maxilla, orthognathic mandible, severe proclination of incisors and crowding were present. It has been evidenced that the rate of tooth movement was normal. Additionally, no abnormal root resorption or bone loss was noticed. In a 7 month follow up also, nothing abnormal was detected. In general, the orthodontic treatment was uneventful and no untoward issues were observed. What still needs to be clarified is how successful would growth modulation procedures, especially advancement of the maxilla, would be in the growing Ach patients?

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