

An Unusual Presentation of An Achondroplastic Patient – with Stress on The Pathogenesis of The Craniofacial Manifestations

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Abstract: Achondroplasia is a most common form of non - lethal skeletal dysplasia dwarfism which manifests as short stature and limb shortening. It exhibits very characteristic craniofacial manifestations hence is of keen interest to the dentists. This paper highlights the unusual craniofacial features in achondroplasia along with emphasis on their pathogenesis.

Keywords: craniofacial, pathogenesis, radiographic manifestations, mandible

I. Introduction

Achondroplasia, first used by Parrot (1878) also known as chondrodystrophia foetalis is a misleading term because cartilage is in fact formed in the disorder; however, the term is well established.^[1] The achondroplasia family, as described by Spranger, also includes the mildly severe hypochondroplasia and the lethal thanatophoric dysplasia(TD). Recently, SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans) dysplasia, a skeletal dysplasia with features of both achondroplasia and TD, has been added to this family of disorders. These other disorders in the achondroplasia family also result from mutations in the FGFR3 gene. The diagnosis can usually be made on the basis of clinical characteristics and specific features on radiographs^[2].

II. Case report

37 years old male patient reported to the department of Oral Pathology and Microbiology with the chief complaint of extra-oral chronic sinus draining pus and blood, over the right maxillary region since since 5-6 months. There was no other medically relevant past history or family history. Patient was born to non - consanguineously married couple, is married and has two children. On examination, extra-orally the sinus opening was of about 2mm * 2mm with a nodule and dimpling of the surrounding maxillary region. (figure 1) Intra- orally patient's teeth were present in buccal vestibule with no occlusion possible. There were over retained E C and missing permanent teeth. Teeth in the involved region were not carious nor showed tenderness. The oral hygiene was poor. (figure 2)

Physical examination of the patient revealed short stature (150 cms), abnormal gait (genu valgum with right leg), thin built and abnormalities with the vertebral column. Craniofacial examination showed large head compared to the face tilted on right side, coarse facial features, frontal bossing, mid facial flattening with absent malar prominence, relative mandibular prognathism. The following haematological and biochemical parameters were normal: complete blood count, renal and liver function tests, alkaline phosphatase, electrolytes. IOPA and OPG of the involved region showed no lesions whereas OPG of the patient revealed hypoplastic maxilla & mandible with totally absent alveolar bone, impacted 13, 15, 43, 44, 47 and thin condyloid and zygomatic processes with deepening of the sigmoid notches. (Figure 3) CT scan of the patient revealed platybasia, (figure 4) hypoplasia of maxilla and mandible, retrognathic maxilla, J shaped sella tursica, (figure 5) hypoplastic maxillary and frontal sinuses, (figure 6 & 7) generalised severe osteopenia, multiple cervical vertebrae anomalies with posteriorly displaced ligament of dens likely suggestive of atlanto-axial instability and anterior wedging of the lumbar vertebrae. (figure 8) On the basis of clinical and radiographic features diagnosis of achondroplastic individual with chronic suppurative osteomyelitis was given.

The lesion of patient was treated first by phase I conservative therapy, scaling and polishing. Antibiotics were prescribed after culture and sensitivity of draining pus (enterobacteria species sensitive to colistin), but the lesion persisted. Therefore, CBCT was performed to learn about the lesion using gutta percha cone in the sinus tract. Sinus tract could be traced leading to right maxillary posterior teeth with slight diffuse radiolucency traced in one slice but the localisation wasn't possible due to severe crowding of teeth. Extraction of the impacted and deciduous teeth was done in the involved region along with excision of sinus tract. Histopathologically necrosed bone was evident at places. (figure 9) Focal area showed periapical granuloma undergoing cystic change.(figure 10) Ankylosis of deciduous teeth was evident as well. (figure 11) The surgery

and healing of the patient was uneventful. The patient again reported with pus discharge and pain in lower anterior teeth after 2 years. Later the patient underwent total extraction due to recurrent infections and poor prognosis of teeth.

III. Discussion

Achondroplasia, most common of the nonlethal bone dysplasias has been estimated as ranging between 1/16,000 and 1/35,000 live births. Clinical features of achondroplasia include short stature with normal trunk length, rhizomelic shortening of the extremities, bowing of the lower extremities, short stubby trident hands, spinal stenosis and lumbar lordosis. Craniofacial characteristic of this disorder include macrocephaly, platybasia, prominent forehead, depressed nasal bridge, maxillary hypoplasia, otolaryngeal system dysfunction, and foramen magnum stenosis.^[1,3] Oral features like malocclusion, delayed eruption, oligodontia, open bite etc have been previously reported in achondroplasia. Dunbar et al. (1980) concluded that the main orthodontic problem in achondroplasia is class III malocclusion also seen in the reported instance. Early orthodontic evaluation should be considered in achondroplastic children, literature reported successful orthodontic treatment in achondroplastic children with or without orthognatic surgery^[3]. The current case however, had prolonged neglected oral health and had not undergone any treatment leading to the presented severe manifestations.

More than 80% of recorded cases of achondroplasia are sporadic as in the present case, representing new mutations. Increased paternal age at time of conception is associated with sporadic cases. Among the familial cases, autosomal dominant inheritance can be demonstrated. Achondroplasia is caused by mutation in fibroblast growth factor 3 (FGFR3) on chromosome 4, causing a defect in the maturation of chondrocytes in the cartilage growth plate which enables abnormal cartilage growth-plate differentiation and insufficient bony development.^[4] It has been established that there is mutation in one copy of FGFR3 gene which leads to glycine arginine substitution in the transmembrane domain of the FGFR3. This leads to gain in function of FGFR3 which ultimately causes decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy and cartilage matrix. FGFR3 also plays an important role in cell growth and division, determination of cell type, formation of blood vessels, wound healing and embryo development.

Developmentally the craniofacial skeleton forms by intramembranous ossification except for the base of the skull and secondary cartilages for rapid development. The question then arises, why specific orofacial manifestations should take place when developmentally they are unrelated to cartilage or endochondral ossification?? Does FGFR3 have role in these manifestations?

Maxilla forms entirely by intramembranous ossification post-natally. There is no cartilage for replacement so the growth occurs in two ways

- Apposition of bone at the sutures that connects maxilla to cranium and cranial base
- Surface remodelling

Maxilla is attached to anterior end of cranial base, thus lengthening of cranial base pushes it forward. Pattern for growth of the face is “out from under cranium” which is achieved by push from cranial base growth and growth at the sutures. Thus, defect in the cranial base formation can lead to ‘dished in’ appearance of midface i.e. mid face deficiency.^[5]

Ravi MS conducted a study to compare individuals with prognathic maxilla, retrognathic maxilla with normal maxilla and evaluated the FGFR3 mutations in these individuals. They concluded that the two commonly occurring specific mutations causing achondroplasia have no role to play in the morphology of maxilla in the selected individuals. Studies are required to sequence the complete gene in order to evaluate the presence of any novel mutation sites in the FGFR3 gene that can be attributed to the morphology and growth of maxilla^[6].

Achondroplasia occurs as a result of early closure of the speno - occipital suture. Early closure of suture at the skull base accounts for the small foramen magnum, short cranial base and J-shape sella turcica. Small foramen magnum is also attributed to the reduced growth of the occipital bones due to the underlying genetic defect. The length of anterior cranial base is normal in achondroplasia whereas, the posterior length is shorter than normal. Thus there is a compensatory over expansion of the skull vault and frontal region to accommodate expanding brain leading to enlarged calvarias and frontal bossing.^[7] Macrocephaly may be secondary to hydrocephalus. Hydrocephalus may be due to venous outflow obstruction at the, jugular foramen level, leading to elevated venous pressure and reduced flow in the superior sagittal sinus. The lack of resorption in the arachnoid villi because of these pressure effects produces large amount of CSF in the ventricles, increased intra cranial pressure maintenance of wider cranial sutures and an enlarged head.^[8]

Relative mandibular prognathism and Class III malocclusions have been described in achondroplasia. Because condylar cartilage is the product of periosteal chondrogenesis (Meikle, 1973), mandibular growth is not affected.^[3] Until recently it was believed that mandibular growth is normal in achondroplasia and only

endochondral ossification is affected whereas now studies have proven that the shape and position of mandible are also affected and to some extent intramembranous bone development as well.^[9]

Havens et al (2008) studied the chick mandibles and concluded that it led to reduced proliferation, increased apoptosis, and decreased differentiation of chondroblasts in Meckel's cartilage. These changes resulted in the formation of a hypoplastic mandibular process and truncated Meckel's cartilage. Their intervention also affected the proliferation and survival of osteoprogenitor cells in osteogenic condensations, leading to the absence of five mandibular bones in the chick embryo. Several FGF and FGF receptors are expressed in the mandibular epithelium and mesenchyme (reviewed by Nie et al., 2006). The consequences of perturbations in components of FGF/FGFR signaling have revealed essential roles of FGF signaling in several aspects of mandibular morphogenesis, including mediating growth-promoting epithelial-mesenchymal interactions, formation of pharyngeal pouches, and survival of mandibular mesenchyme. FGFR3 signaling is required for the elongation of Meckel's cartilage, and FGFR2 and FGFR3 have roles during intramembranous ossification of mandibular bones.^[10]

Duplan et al (2014) then studied CT scans of 16 achondroplastic patients and found that the condyles were shorter, broader and projected forward. Further his mice studies revealed that mandibles had shorter bodies; condyles, angle and mental protuberances were underdeveloped. Meckel's cartilage and mandibular secondary cartilages showed abnormal proliferation and differentiation of chondrocytes and the replacement of Meckel's by bone was also delayed.^[9] Thus, the mandibular defects and absence of alveolar bone in the present case can be justified.

The dentition in the achondroplasia is usually said to be normal, however delayed eruption of both dentition, oligodontia, and absent teeth have been reported due to altered bone development. Whereas, multiple over-retained deciduous teeth, ankylosed deciduous and impacted permanent teeth had not been reported in achondroplasia.^[3] The FGFs are reported to have roles in teeth development as well, whereas studies of FGFR3 on normal odontogenic apparatus did not reveal any such positivity. However, Britto JA (2001) showed FGFR1, FGFR2, and FGFR3 equal expression throughout the predifferentiated mesenchyme of the cranium, the endochondral skull base, and midfacial mesenchyme at 8 weeks of gestation. By 10 to 13 weeks, FGFR3 was maximally expressed in dental epithelia and proliferating chondrocytes of the skull base, but poorly expressed in the osteogenic tissues of the midface.^[11] These findings may have implications in dentition development in achondroplasia. Recurrent dental infections in these individuals leading to total extraction are also not reported.

IV. Conclusion

Thus, the present case adds to the pre - existing knowledge about achondroplasia and also supports the notion of mandibular and intramembranous bone formation defects. This paper also aims at highlighting the importance of interceptive orthodontics and timely dental treatment in these individuals

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Figures:

Figure 1 – Extraoral draining sinus with dimpling of surrounding skin. Large head with coarse facial features, mid facial flattening and frontal bossing



Figure 2 – Intraorally teeth placed in buccal vestibule, poor oral hygiene, over retained right upper E missing 15



Figure 3 - Hypoplastic maxilla & mandible, reduction in alveolar bone and basal bone, impacted 13, 15, 43, 44, 47 Short & malformed roots with 17, 26, 27, 46, 47



Figure 4 - Platybasia

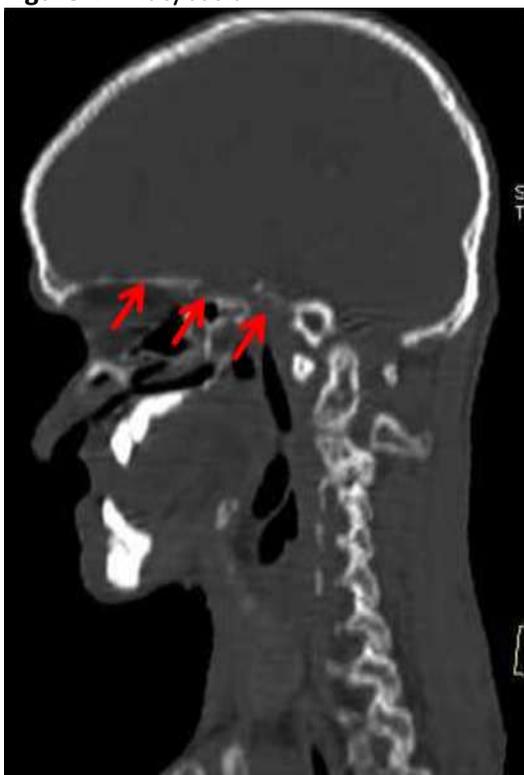


Figure 5 –Retrognathic maxilla, hypoplastic maxilla and mandible, elongated sella



Figure 6 – Hypoplastic frontal sinus

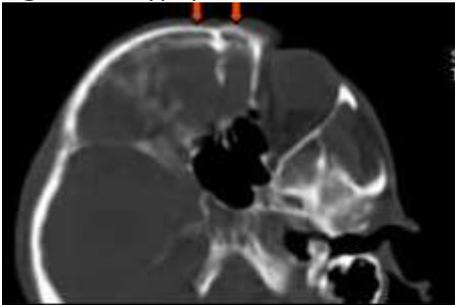


Figure 7 - Hypoplastic maxillary sinus

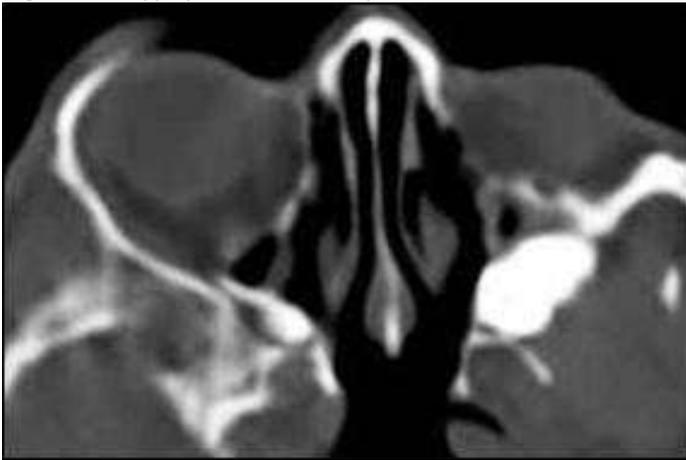


Figure 8 – Generalised severe osteopenia, anterior wedging of T10 and T11 vertebrae



Figure 9 – Necrosis of bone seen adjacent to the teeth



Figure 10 – Periapical granuloma undergoing cystic change

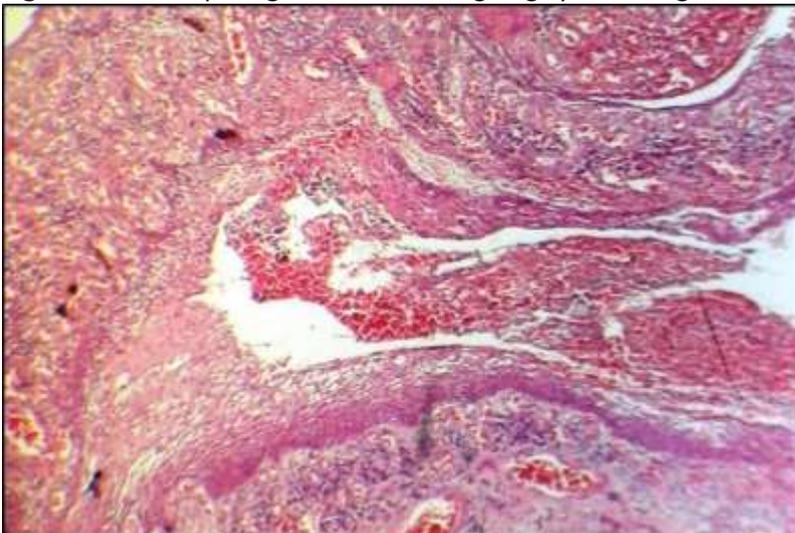


Figure 11 – Ankylosis of the tooth with the surrounding bone

