

## CASE REPORT

# Orofacial findings in postaxial acrofacial dysostosis

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**ABSTRACT**

We report a new case of postaxial acrofacial dysostosis (Miller) syndrome with expanded profile. The patient presented with unusual orofacial and digital anomalies along with mental retardation. This report emphasizes the recognized features of the syndrome as well as describes intraoral findings that could aid in the diagnosis and management of these patients.

**Key words:** Acrofacial dysostosis, Miller's syndrome, Treacher Collin's syndrome

## INTRODUCTION

The acrofacial dysostoses (AFDs) are a clinically heterogeneous group of conditions characterized by mandibulofacial dysostosis and a variety of limb anomalies. Depending on the type of limb defects, AFD can be classified into two major groups: Nager syndrome and Miller's syndrome. Nager syndrome comprises mandibulofacial dysostosis and preaxial limb defects. The limb defects are typically limited to the upper limbs and are asymmetric. Miller's syndrome patients have craniofacial features similar to those of Nager syndrome and are characterized by postaxial reduction defects of the upper and, sometimes, the lower limbs. Other forms of postaxial AFDs have been described as Weyers' AFD,<sup>[1]</sup> AFD-type Arens<sup>[2]</sup> and postaxial AFD with vertebral defects.<sup>[3]</sup> Out of these, Miller's syndrome is the most common subtype. The reason for presenting this case is twofold: first, the phenotypic features in this case do not fit the classical Miller's syndrome; second, the intraoral manifestations have not received much attention in the published cases of acrofacial dysostosis.

## CASE REPORT

An 8-year-old boy born to young, healthy and non-consanguineous parents reported with abnormal craniofacial, oral and digital findings. Antenatal and birth history were normal. Birth weight was 2500 g and length was 50 cm. Family history was negative with regard to congenital malformations, mental illness, skeletal anomalies and miscarriages. Abnormal facial features and missing toes were noted soon after the birth

but inability to hear was noticed at a later stage. At 2 years of age, delay in reaching the developmental milestones was noticed and the patient started walking by two and half years of age. Hearing deficit was corrected by cochlear implant at 2 years and 9 months of age.

At the age of 8 years, he presented to the dental department with the chief complaint of multiple missing teeth. On examination, dyscephaly with frontal bossing, mild malar and mandibular hypoplasia, hypertelorism, broad nasal root, down-slanting palpebral fissures, macrostomia, low set ears, choanal atresia, hypoplastic alae nasi, long philtrum and a thin-pinched nose were noted. Digital anomalies included absence of third, fourth and fifth toes and syndactyly in the left foot. Other limbs were normal. Intelligence quotient IQ was found to be below normal in the range of 45-50 and he showed poor response to the surroundings.

On intraoral examination, a high palatal vault, oligodontia, enamel hypoplasia, high frenal attachment in maxilla and ankyloglossia were noted. Panoramic radiograph showed multiple missing permanent teeth including maxillary and mandibular lateral incisors and canines. Tooth germs for all the permanent second and third molars were absent [Figure 1a-d].

Investigations carried out included radiological examinations, routine hematological investigations, ultrasonography of abdomen, echocardiography, electroencephalogram and karyotyping. The anteroposterior (AP) skull view revealed dyscephaly with frontal prominence. Foot-ankle radiograph revealed agenesis of third, fourth and fifth toes and syndactyly involving the first and second toes with complete soft tissue fusion without bony fusion [Figure 2a and b]. There was no abnormality noted in the radiographs of the upper limbs, chest and of the lumbosacral region of the spine.

Investigations including computed tomography (CT) head, magnetic resonance imaging (MRI) brain,

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10.4103/0973-029X.131947

electroencephalography (EEG) and electrocardiography (ECG) were done and were found to be within normal limits. The cytogenetic profile of the patient was normal and no chromosomal anomalies could be detected [Figure 2c]. Family history was inconclusive. The patient was born from a non-consanguineous marriage and had no siblings. A multispecialty approach was advocated to treat the patient. Oral rehabilitation was done using prosthetic appliances. Frenulectomy was advised for the correction of ankyloglossia.

**DISCUSSION**

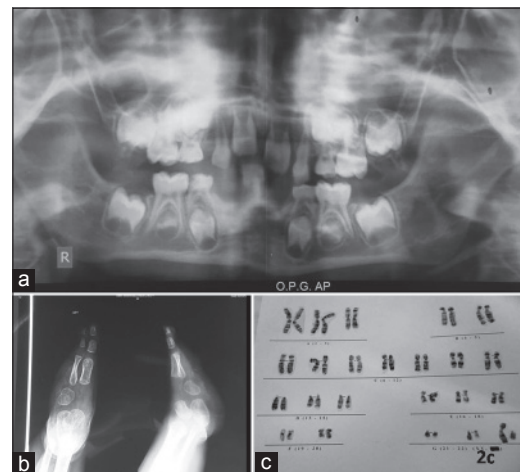
The AFDs are heterogenous disorders characterized by a combination of varying severities of mandibulofacial dysostosis with preaxial or postaxial limb abnormalities. Postaxial acrofacial dysostosis (Miller) syndrome is rare and is apparently inherited as an autosomal recessive trait. The syndrome was first described by Genee<sup>[4]</sup> in 1969, Wiedemann<sup>[5]</sup> in 1973 and as a complete clinical entity by Miller *et al.*, in 1979.<sup>[6]</sup> With only 34 cases having been published till 1993<sup>[7]</sup> and not more than 50 cases till now, the postaxial acrofacial dysostosis appears to be rare. It is caused by dysfunction of the *DHODH* (dihydroorotate dehydrogenase) gene, which encodes a key enzyme in the pyrimidine *de novo* biosynthesis pathway and is localized at mitochondria intermembrane space. The mutant gene responsible for the disorder has been found recently to be *DHODH*, which is located at chromosome 16q22.<sup>[8]</sup> A total of 13 mutations in the *DHODH* gene have been reported in Miller’s syndrome, from exon 2 to exon 9.<sup>[8,9]</sup> However, it is unknown how mutations in *DHODH* cause the phenotype of Miller’s syndrome.

The predominant features are Treacher Collins-like facies and limb deficiencies, although the heart, gastrointestinal tract, urinary tract and skin may also be involved. The craniofacial manifestations include malar hypoplasia, coloboma of eyelids, down-slanting palpebral fissures, ectropion, hypoplastic ears, hearing deficit, micrognathia and cleft lip/palate. The limb defects predominantly involve the postaxial ray, with a wide range of severity and to a lesser extent the preaxial ray. Postaxial limb deficiency, syndactyly and abnormal ulna/radius are noted. Intelligence is usually normal. The presence or absence of these findings in the presented case has been described in Table 1.

Miller *et al.*, in 1979 described patients with postaxial limb deficiency, cup-shaped ears and malar hypoplasia. Donnai *et al.*, in 1987<sup>[10]</sup> described 10 patients (seven reviewed published cases and three personal unpublished observations). Malar hypoplasia and lower lid ectropion were found in all patients. Cleft palate was present in nine out of 10 cases, cleft lip only in two cases. Seven out of 10 patients had bilateral absence of the fifth digit, including the fifth metacarpal and the others showed unilateral aplasia or hypoplasia of the fifth digit. Most had shortened forearms and radiological evidence of ulnar hypoplasia. The fifth toes were absent in all the cases and occasionally the third and fourth toes as well, as seen in this case. Intelligence seemed to be normal and autosomal



**Figure 1:** (a) Extraoral view showing frontal bossing, hypertelorism, wide nasal bridge and macrostomia; (b) Profile view showing cochlear implant and beak-shaped nose; (c) Intraoral view showing oligodontia and ankyloglossia; (d) Lower limbs showing missing toes and syndactyly



**Figure 2:** (a) Orthopantomogram showing agenesis of multiple permanent teeth; (b) Foot-ankle radiograph of the left foot showing agenesis of toes and syndactyly; (c) Karyotype showing normal cytogenetic profile

**Table 1: Clinical features of postaxial acrofacial dysostosis**

Clinical features reported	Present case
Malar hypoplasia	+
Mandibular hypoplasia	+
Cleft lip/palate/high-arched palate	+
Downslanting palpebral fissures	+
Cupped ears	-
Hearing deficit	+
Choanal atresia	+
Lower lid ectropion	-
Coloboma of eye lids	-
Postaxial limb deficiency	+
Syndactyly	+
Accessory nipples	-
Cardiac, gastrointestinal and genitourinary anomalies	-

recessive inheritance is possible. Additional reports by Fryns and Van den Berghe in 1988<sup>[11]</sup> and Chrzanowska *et al.*, in 1989<sup>[12]</sup> described patients manifesting similar phenotypic features as described by Miller *et al.*, (1979) but with minor differences. Sulko *et al.*, in 2008<sup>[13]</sup> described a patient with postaxial limb defects associated with symmetrical ulnar and fibular bone absence in hands and feet.

The intraoral findings in patients suffering from acrofacial dysostosis syndrome have not received much attention. The present case suffered from oligodontia, enamel hypoplasia and ankyloglossia, which have not been reported in the literature. The extra features in this patient not only broaden the phenotype of Miller's syndrome but also emphasize the need to pay due attention to intraoral features in diagnosing various syndromes. Further evidence is required to relate these dental anomalies to Miller's syndrome.

Treacher Collins syndrome and Nager syndrome have similar facial features but the former has no limb anomalies and the latter has radial ray defects. The present case could be considered as a new variant of Miller's syndrome.

## CONCLUSION

Thus, few rare syndromes are difficult to diagnose when they present features that are not ascribed classically to the syndrome. In such situations, a thorough clinical examination, along with radiological investigations and genetic analysis becomes essential to reach a diagnosis. Further care of patients may require coordinated collaborative efforts of professionals belonging to different specialities to facilitate effective and appropriate care to the affected patients.

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**How to cite this article:** Urs AU, Kumar P, Nunia K. Orodonal findings in postaxial acrofacial dysostosis. *J Oral Maxillofac Pathol* 2014;18:149.  
**Source of Support:** Nil. **Conflict of Interest:** None declared.