Clinical Case Reports

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CASE REPORT

# Acromelia-oligodontia syndrome

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**Funding Information**
University of Marburg, Germany, National Institutes of Health (HL090648).

Received: 2 June 2016; Revised: 16 December 2016; Accepted: 5 March 2017

***Clinical Case Reports*** **2017; 5(6): 968–974**

doi: 10.1002/ccr3.956

## Key Clinical Message

This case report describes a patient with ankyloglossia, oligodontia, unilateral hypoplasia of the zygoma and mandible, along with bilateral distal reduction anomalies of his limbs without long bone abnormalities. This may represent a mild variant of oromandibular limb hypogenesis syndrome, expanding the phenotypic spectrum, or a previously unrecognized malformation syndrome.

## Keywords

Acromelia, ankyloglossia, oligodontia, oromandibular limb hypogenesis syndrome, orthopantomograph, pleiotropy

## Introduction

Polymalformation syndromes can be caused by mutations in pleiotropic genes. Pleiotropy can result from defects in proteins with multiple biochemical functions. Alternatively, pleiotropic genes may be required for fundamental cellular functions necessary for the development of multiple tissues or organs [1]. For example, the neural crest gives rise to structures of the face, cardiac outflow tract, peripheral nervous system, and pigment cells. Thus, mutations in genes required for neural crest development cause multi-organ phenotypes [2]. Similarly, cilia are required for multiple developmental pathways and for the homeostasis of several organs. Therefore, defects in genes required for ciliary function lead to a range of diseases with either specific or broad systemic involvement [3].

Oral, facial, and distal limb anomalies have been described in a range of disorders, including oromandibular limb hypogenesis syndrome (OMLHS) [4] (also known as Hanhart syndrome, OMIM # 103300), oral–facial–digital syndrome (OFDS) [5] (OMIM # 311200), and other rarer malformation syndromes with distal limb deficiencies

including Buttiens-Fryns syndrome (with micrognathia) [6] (OMIM # 246560), Adams-Oliver (with scalp defects) [7–9] (OMIM # 100300), and acheiropodia (without oromandibular involvement) [10] (OMIM # 200500). This report describes a patient with oral, facial, and limb abnormalities that show similarities to the above-listed syndromes. Each of the aforementioned disorders was considered in the initial differential diagnosis. However, after review of the literature, the apparently unique combination of characteristics in this case suggests a mild variant of oromandibular limb hypogenesis with features that expand its phenotypic spectrum.

## Materials and Methods

### Case report

Informed consent along with the written authorization was obtained from the patient at the Government Dental College and Hospital, Vijayawada, India. This young man presented at the dental school clinic for a dental examination at 18 years of age. He was the first child of healthy, unrelated parents. His younger brother was healthy. Congenital distal skeletal anomalies of both the upper and lower limbs were identified at the time of birth. During pregnancy, there was no known exposure to teratogens or other maternal factors relevant to the observed deformities. All the developmental milestones were normal. Growth parameters remained within the normal range. His growth parameters were the following: height 177.8 cm (~55th percentile), weight 66.8 kg (35th percentile). Body mass index was 21.1 (35th percentile). The patient, a college student at the time of examination, was of normal intelligence.

Frontal photograph of the patient's face (Fig. 1A) revealed facial asymmetry with left malar and mandibular hypoplasia, with the chin deviated to the affected side. Maxillary view (Fig. 1B) showed a high-arched palate and palatally erupted maxillary left second premolar. Mandibular view (Fig. 1D) showed ankyloglossia/tongue-tie, which resulted in restricted tongue movement. Except for the attachment of lingual frenulum to the mandible, tongue development was normal and surgical correction of the tongue-tie resulted in normal tongue movement as well as improved speech. Oligodontia was evident with congenital absence of the maxillary left third molar. Additionally, the mandibular left central incisor, canine, second premolar, first, second, and third molars (with no history of extractions), and right central incisor were also missing. There was also a retained mandibular left canine. An orthopantomograph (Fig. 1C) supported the observed clinical findings, reduced height of mandible on the left side and missing posterior teeth on the same side. A supernumerary tooth between maxillary left premolars and an impacted tooth between right mandibular premolars, along with bifurcated styloid processes on both sides (but prominent on left side), was evident from the orthopantomographic image. An edentulous ridge on the left mandibular arch and reduced alveolar ridge height were visualized on study models (Fig. 1E).

The hands were absent (Fig. 1F) except for a rudimentary thumb with a skin tag. On palpation, carpal bones were not well delineated and one digit on both sides was present. Radiographic findings (Fig. 1G) revealed the presence of a rudimentary thumb at the distal aspect of both the left and right upper limbs, with a single phalanx attached to the lateral surface of the distal radius. Absence of carpals, metacarpals, and phalanges except for two carpals on the left, one of which was a fused carpal bone, was found on the radiograph of the distal upper extremity. Both forefeet (Fig. 1H) were absent, and on the right side, a small fifth toe was present. A lack of segmentation of tarsal bones, absence of metatarsals (except for rudimentary second metatarsal on the right side), and absence of phalanges (except for presence of part of a great toe) were noted clinically. Radiographic findings of the feet (Fig. 1I) included only two tarsals and the absence of all the metatarsals and phalanges on the left side. On the right side, four deformed tarsals were present, but all the metatarsals were absent (except for the rudimentary first metatarsal) and a single phalanx was also noted.

### Clinical evaluation method

Clinical facial analysis was used for the assessment of facial asymmetry in this patient. The glabella, tip of the nose, midpoint of philtrum of upper lip, and the midpoint of the chin were marked to establish the facial midline. Next, the inner and outer canthi of the eye, the ala of the nose, tragus of the ear (top of the external auditory canal), superior and inferior, anterior and posterior points on the external ear, angle of the mandible, and the midpoint of condyle of the mandible were marked on both the right and left sides of the face. The distances between anatomic landmarks were measured using a thread and a scale ruler as follows: (1) external ear, superioinferior; (2) external ear, anteroposterior; (3) midpoint of bridge of nose to inner canthus of eye; (4) midpoint of bridge of nose to outer canthus of eye; (5) tip of the nose to ala of the nose; (6) tip of the nose to upper tragus of the ear (top of the external auditory canal); (7) midpoint of philtrum of upper lip to angle of the mandible; (8) midpoint of chin to angle of the mandible; (9) angle of the mandible to midpoint of condyle. An orthopantomographic X-ray image and study models were obtained to visualize dental anomalies. Dental casting stone and

 

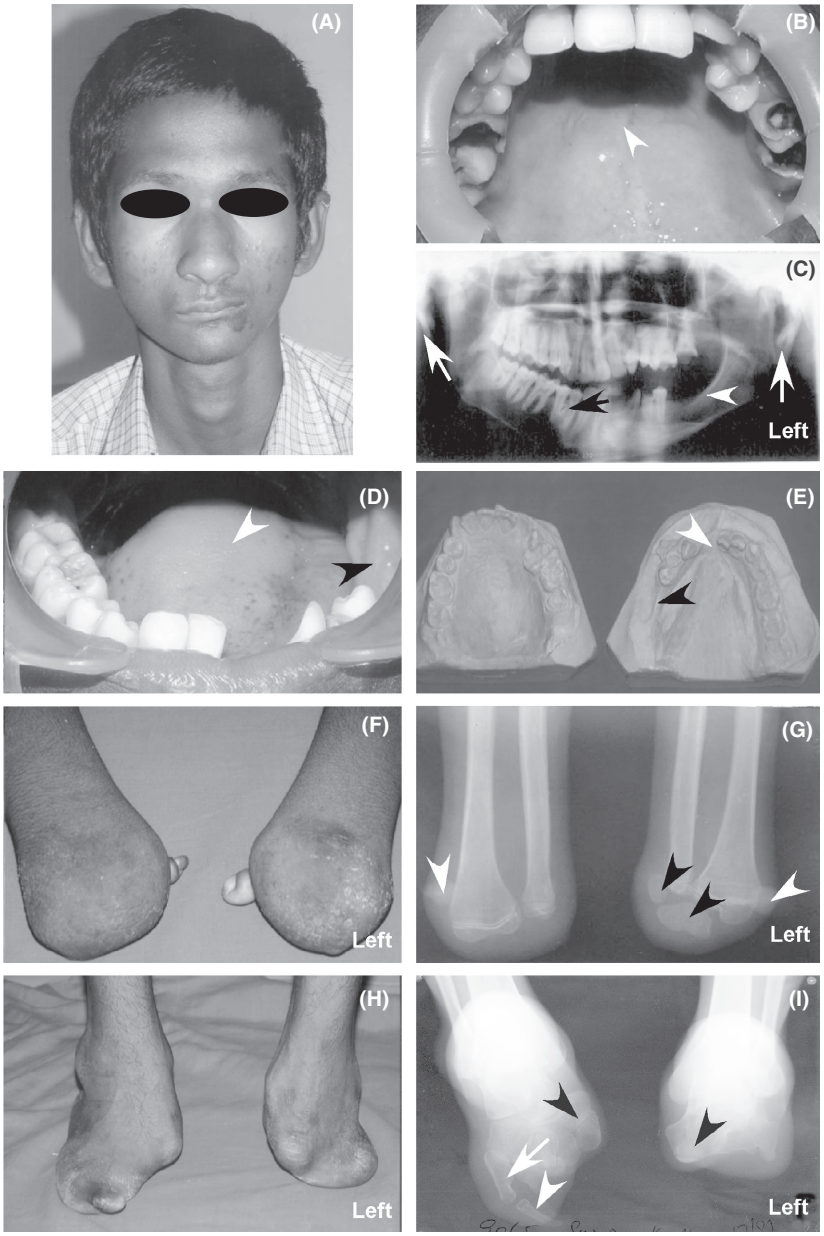


**Figure 1.** Clinical and radiological characteristics: (A) Facial features include zygomatic and mandibular hypoplasia on the left, deviation of the chin to the left, high forehead, and blepharophimosis. (B) Maxillary view of the oral cavity shows high-arched palate (white arrowhead). (C) Orthopantomographic X-ray image illustrates bifurcated styloid process on both sides (white arrows); a supernumerary tooth between the first and second maxillary premolars on the left; missing mandibular teeth on the left (white arrowhead); and an end-on-view of supernumerary tooth between the first and second mandibular right premolars (black arrow). (D) Mandibular view of the oral cavity shows reduced elevation of tongue (white arrowhead) due to ankyloglossia (tongue-tie), and missing teeth with hypoplastic mandibular ridge on the affected side (black arrowhead). (E) Study models demonstrate maxillary high-arched palate; mandibular edentulous ridge and reduced height of alveolar ridge associated with missing teeth on the left (black arrowhead); lingual frenulum attached to mandibular alveolar ridge (white arrowhead). (F) Clinically, the forelimbs show rudimentary thumbs and acromelia. (G) Radiograph of the forelimbs demonstrate the absence of most carpals except for two (black arrowheads), one which was fused and the absence of metacarpals and phalanges on the left hand; total absence of all the carpals, metacarpals, and phalanges on the right hand; rudimentary thumbs with single phalanx attached to lateral surface of lower end of radius on both hands (white arrowheads). (H) A clinical photograph of the lower limbs shows absent forefeet, presence of a rudimentary toe on the right leg, lack of segmentation of tarsal bones. (I) Radiographic image of the feet illustrates the presence of only two tarsals, absence of all the metatarsals and phalanges on the left foot (black arrowhead), presence of deformed tarsals (black arrowhead), absence of metatarsals except for a rudimentary first metatarsal (white arrow), and the presence of a single phalanx (white arrowhead) on the right leg.

rubber molds were used to prepare the study models from the dental impressions taken using a generic brand of alginate, an irreversible hydrocolloid elastic impression material, and dental impression tray. Radiographic images were taken to document limb anomalies. Abdominal and renal ultrasonography evaluations were performed.

### Cytogenetic and molecular studies

Metaphase G-banded karyotype was performed using standard methods. DNA was isolated from peripheral blood. Mutational testing of all coding exons in *GLI3* was performed by single-strand conformation analysis and sequencing of genomic amplimers [11, 12]. *LMBR1* was analyzed for homozygous deletions of exons 3–5 by PCR with electrophoresis of restriction fragments. Next, mutation analysis using PCR and bidirectional sequencing of exons 1–16 was performed [10]. All mutational studies were performed for both the patient and his mother. The father died as a result of a workplace accident, and therefore, no DNA was available for study.

## Results

### Clinical investigation results

Clinical facial analysis was performed with direct and photographic methods to assess facial asymmetry, using anatomic landmarks. Measurements of facial distances from the midline were reduced by two to four mm on the affected (left) side relative to the right side of the face, for measurements "f" through "i" (as above in Clinical evaluation method). These measurements supported the clinical observations that the zygomatic bone was flatter, and the height of the mandible was reduced on the left side and that the chin was deviated to the affected side. Previously published normative data [13] demonstrated that two standard deviations of signed asymmetry of normal human faces range 4–5 mm. Because the quantitative data from this patient's soft tissue dentofacial analysis did not exceed two standard deviations from the mean, the facial asymmetry in this case was not statistically significant. The skull and chest radiographs were normal. Ultrasonography of the upper abdomen showed normal kidneys and other internal organs.

### Molecular and cytogenetic results

Cytogenetic analysis of phytohemagglutinin-stimulated peripheral blood lymphocytes revealed a normal male karyotype with no numerical or structural abnormalities. Because of the coexistence of facial and limb anomalies, a known characteristic of Greig cephalopolysyndactyly syndrome, *GLI3* was analyzed in this patient, but no mutation was found. *LMBR1* was examined for mutations because this patient showed limb reduction anomalies that were similar to acheiropodia. However, no deletions or point mutations were found in *LMBR1*.

## Discussion

The clinical and radiographic findings suggest that this patient's phenotype likely falls within the spectrum of oromandibular limb hypogenesis syndrome. Other acromelia-associated syndromes were considered for the differential diagnosis, including the Adams-Oliver syndrome [7–9] (OMIM # 100300), acheiropodia (handless–footless families of Brazil) [10] (OMIM # 200500), Greig cephalopolysyndactyly syndrome (GCPS) [14] (OMIM # 175700), Buttiens-Fryns syndrome [6] (OMIM # 246560), oral–facial–digital syndrome, type I (OFDS-I) [5] (OMIM # 311200), and aglossia-adactylia/Hanhart syndrome [4] (OMIM # 103300). Table 1 compares the clinical features of this case with the clinical features of the above-mentioned group of diseases.

Adams-Oliver syndrome [7–9] has an extremely variable phenotype with congenital distal limb reduction defects associated with scalp defects. Whereas Adams-Oliver syndrome is characterized by aplasia cutis congenita and alopecia, which can be localized to any part of the body (trunk, limbs, scalp), these lesions were absent in this patient.

Symmetric distal limb reduction "amputation" abnormalities have been described in acheiropodia and Buttiens-Fryns syndrome. In acheiropodia, bilateral congenital distal mesomelia is found with aplasia of the hands and feet and is caused by a genomic deletion in *LMBR1* [10]. Buttiens-Fryns syndrome is characterized by findings similar to this case in that it has mid-face hypoplasia, bilateral transverse limb reductions with a range of anomalous long bones to normal long bones, and deficient/rudimentary short bones of all four limbs. Although a recent case suggests psychomotor and intellectual development may be normal [15], mild-to-moderate mental retardation and hypoplastic kidneys are obligate characteristics of Buttiens-Fryns syndrome and these findings are absent in this case.

Greig cephalopolysyndactyly syndrome is characterized by craniofacial abnormalities and pre- and post-axial polysyndactyly of the hands and feet and is caused by *GLI3* mutations. Thus, both the limb anomalies and the molecular cause of GPCS appear to be distinct from this case. This case of acromelia-oligodontia syndrome (AOS) also has some shared features with OFDS-I, but lacks several lesions characteristic to OFDS-I, including clefts of the lip and/or palate, CNS malformations, and association

 

**Table 1.** Summary of clinical features seen in aglossia-adactylia, hypoglossia-hypodactylia, oromandibular limb hypogenesis, and Hanhart syndrome [19], compared to our patient.

| Reference (AAS/HHS, OMLHS/HS) | Tongue | Cleft Palate | Mandible abnormalities | Rt.UL* | Lt.UL* | Rt.LL* | Lt.LL* | Other malformations |
|---|---|---|---|---|---|---|---|---|
| De Jussieu** (1718, 1719) [Republished 1770]: AAS/HHS | +++ | – | – | – | – | – | – | – |
| Spiller** (1816–1838) [early 19th century]: AAS/HHS | +++ | – | – | – | – | – | – | Almost entire absence of soft palate except for two lateral rudiments |
| Kettner** (1907): AAS/HHS | ++ | +++ | – | + | + | ++ | ++ | – |
| Rosenthal [20]: AAS/HHS | +++ | – | + | +++ | + | ++ | – | Cleft lip, slight protrusion of intermaxillary region; small lower jaw; hypodontia; large tonsils divided into upper and lower lobes; folded epiglottis |
| Nevin et al. [21]: AAS/HHS | + | ++ | ++ | – | + | + | + | Lower lip |
| Nevin et al. CASE-1 [22]: AAS/HHS | ++ | – | – | + | + | +++ | + | Heart murmur, ischemic heart disease |
| Nevin et al. CASE-2 [22]: AAS/HHS | ++ | – | + | ++ | ++ | ++ | ++ | – |
| TuncbilekCASE-1 [23]: AAS/HHS | ++ | – | ++ | + | + | +++ | – | – |
| TuncbilekCASE-2 [23]: AAS/HHS | ++ | – | – | – | – | – | – | – |
| TuncbilekCASE-3 [23]: AAS/HHS | +++ | – | ++ | – | – | – | – | Very large low set ears posteriorly rotated |
| Robinow.CASE-1 [Mobius syndrome] [24]: AAS/HHS | ++ | – | ++ | + | + | + | +++ | Sixth and seventh nerve palsies |
| Robinow.CASE-2 [24]: AAS/HHS | + | – | – | + | + | + | + | Intestine (apple peel bowel) |
| Robinow.CASE-3 [24]: AAS/HHS | ++ | – | ++ | + | + | + | + | Single kidney |
| Salles [17]: AAS/HHS | ++++ | – | +++ | – | – | – | – | Bilateral buccal crossbite, excessive overjet, deep bite, high vaulted palate |
| Bokesoy et al. [25]: OMLHS/HS | +++ | ++ | ++ | ++ | ++ | +++ | +++ | – |
| Grippaudo et al. [16]: OMLHS/HS | ++++ | – | +++ | + | ++++ | + | ++++ | Tight lower lip and severely hypoplastic, abnormal temporomandibular joint & restricted mouth opening |
| Robertson et al. [4]: OMLHS/HS | +++ | – | +++ | + | ++++ | + | ++++ | – |
| Our Patient | – | – | +/– | +++ | +++ | ++ | +++ | Ankyloglossia, normal tongue size and function; oligodontia; left zygomatic and mandibular hypoplasia. |

Tongue anomalies: complete absence (++++), tiny wart-like/rudiment (+++), one-third of the tongue hypoplastic (++), mild-to-moderate hypoglossia/microglossia (+), absence of hypoplastic tongue (–). Complete cleft palate: severe (+++), moderate (++), absence of cleft palate (–). Mandibular malformation/hypoplasia: severe (+++), moderate/micrognathia (++), retrognathia (+), unilateral involvement of mild hypoplasia (+/–). *Limb anomalies: right (Rt.) and left (Lt.) upper limb (UL) and lower limb (LL), syn/brachy/ectrodactyly to peromelia at phalangeal level (+), peromelia at metacarpal/metatarsal level (++) & carpal and tarsal levels (+++), involvement of long bones (++++). **Cited in [20].

of polycystic kidney disease (PKD). Moreover, OFDS-I is characterized by digital abnormalities only, whereas in this case the proximal elements of the hands and feet are affected.

The constituent disorders of the oromandibular limb hypogenesis group are distinguished from this case in that they are typically associated with aglossia or hypoglossia (Table 1), which were not found in this patient. However, the limb anomalies of patients with oromandibular limb hypogenesis syndrome (OMLHS) [16, 17] are extremely variable ranging from hypo/syn/brachy/ectrodactyly to peromelia of long bone(s) (mesomelic limb deficiency)

and are associated with moderate to severe malformations of the tongue. Although extremely mild hypoplasia of the tongue may be undetectable in OMLHS [18], this patient had no clinical evidence of hypoplasia of the tongue. The distinct features of oligodontia, unilateral hypoplasia of the mandible, and a hypoplastic zygoma either expand the phenotype of OMLHS, or identify a new syndrome, provisionally called acromelia-oligodontia syndrome.

## Acknowledgments

We would like to thank Dr. Rick Martin who was at Saint Louis University when he provided his insights about this case; Anu Radha Udumudi, Gene Tech, Hyderabad, India, for support and encouragement; the University of Marburg, Germany, for the funding of molecular genetic analysis. Special thanks to Dr. Earl C. Beeks Jr. and Dr. Esther M. Beeks for their support and Dr. Marie M. Tolarova for her insights. We thank the following physicians and health professionals for sharing clinical information with us: Dr. Sayesh Vemuri, Dr. Rupa Nadendla, of Government Dental College and Hospital, Vijayawada, India; Dr. Krishna Rao, Cardiology, Dr. Prabhakar, E.N.T, and Dr. Somanatham, Orthopedics of Siddhartha Medical College and Hospital, Vijayawada, India; Dr. T. Rajendra Prasad, Radiologist, ABC Imaging Center, Vijayawada, India. Special thanks to Mr. T.L. Mohan Rao, Mrs. N. Usha Rani, Mr. Venkat S.R Yarlagadda, Mr. Satish Nadella, Dr. Pratima, Ashok Kumar.V, Dr. Bindu Tummuru, Dr. Vishwanathan Hucthagowder, and Dr. Bert Callewaert. This study was funded in part by a grant from the National Institutes of Health to Z.U. (HL090648). This work is dedicated to Mr. Lakshmi Mohan Rao Talasila and Mrs. Usha Rani Nagabhairava.

## Conflict of Interest

None declared.

## Authorship

All of the authors: reviewed and approved the submission of this manuscript to the journal. JT: was responsible for direct interaction with the patient and his family, consenting, data preparation and manuscript drafting, and table and figure preparation as well as clinical facial analysis, and coordinating input from the authors. RP: provided methodological guidance for the clinical facial analysis, performed the lingual frenectomy, and gave advice on further genetic studies. KVSNY: gave medical advice, analyzed the data, and reviewed radiographic findings. KVSNY: provided advice on case presentation and helped with the referrals for further clinical and radiographic evaluations. RV: provided input on the dental evaluation, analyzed the clinical and radiographic findings, and provided input regarding the case presentation. KHG: performed the genetic study on *GLI3* and *LMBR1*. SKKVS: performed cytogenetic analysis and provided feedback on case study and suggestions on further genetic testing. CMR: provided information from the POSSUM-web database and insights on the similarities between this case and Buttiens-Fryns syndrome. GSG: was responsible for dysmorphology searches of the medical literature, as well as the London Dysmorphology and POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) databases; as a medical geneticist, used clinical records and photographs of patient to identify pertinent clinical features as search parameters for the databases in an effort to identify an already known syndrome; and interpreted the results of the searches and also provided assistance in editing and reorganizing the draft manuscript for final submission. ZU: assisted with the analysis and presentation of the data, provided advice on manuscript preparation, contributed to writing the manuscript, and provided funding for this work.

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