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Oromandibular-limb Hypogenesis Syndrome: A Rare Case Illustrating Shortcomings of Current Classification Systems

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Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in Plastic and Reconstructive Surgery in the Faculty of Health Sciences at the University of the Free State.

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DECLARATION OF AUTHORSHIP

I, Dr Lizanne Small, declare that the coursework Master's Degree Case Report that I herewith submit in a publishable article format for the Master's Degree Qualification in Plastic and Reconstructive Surgery at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

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OLHS – oromandibular-limb hypogenesis syndrome

CN III – cranial nerve III

CNS – central nervous system

ARV – anti-retroviral

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Oromandibular-limb Hypogenesis Syndrome: A Rare Case Illustrating Shortcomings of Current Classification Systems

1. ABSTRACT

Background: Oromandibular limb hypogenesis syndrome (OLHS) includes a spectrum of congenital anomalies that affect the mandible, tongue, and maxilla with or without reductive limb anomalies. Their exact aetiology is unknown and most cases occur sporadic. Several syndromes are included under the umbrella of OLHS with considerable overlap in the phenotypical features between them. Two classification systems that of Hall (1971) and Chicarilli (1985) are currently recognised to classify OLHS. Jung *et al.* proposed a modification of the Chicarilli classification in 2016, but according to the literature this classification has not been used to classify OLHS cases.

Case Presentation: A 3 month old male infant presented with clinical features that straddled more than one syndrome as classified under the OLHS. Given the orofacial and extremity malformations of this case it could be classified as Hall Type IIID *or* VB and Chicarilli Type IV. The aim of this case report was to contribute to understanding the difficulty in the classification of these complex malformations and to review our current classification systems.

Conclusion: Shortcomings in the two most commonly used classifications by Hall and Chicarilli was identified and a classification system proposed by Jung et al in 2016 made classification of this case possible as a Jung Type IV D. As a result from this case report it was clear that a review of current classification systems is needed with the aim to establish a single system that will allow for classification for all the subtypes of OLHS.

2. KEYWORDS

Oromandibular limb hypogenesis syndrome, orofacial and limb abnormalities, Hall classification, Chicarilli classification, Jung *et al.* classification

3. INTRODUCTION

Oromandibular-limb hypogenesis syndromes (OLHS) (OMIM 103300) represent a spectrum of congenital dysmorphic complexes that are characterized by abnormalities of the oral cavity and mandible (including hypoglossia, aglossia, micrognathia, glossopalatine ankylosis, cleft palate, and gingival anomalies) as well as severe asymmetric limb defects (primarily involving distal segments).[1-3]

These malformations are extremely rare with an incidence of 1:175 000 live births and only a few cases have been reported in the literature to date.[1,3]

Several attempts have been made to explain the emergence of OLHS and the interaction of both genetic and environmental factors in the OLHS aetiology are acknowledged in the literature.[3] The majority of cases reported in the literature are sporadic but few have intra-familial history.[4]

Inheritance of mutated *Msx2,* a homeobox gene that is associated with craniofacial and limb malformation, has been proposed but till date, no genetic mutation or chromosomal abnormalities have been identified for this syndrome.[4-7]

Environmental factors likely to be the aetiology are maternal hyperthermia, maternal exposure to radiation and teratogenic drugs, intrauterine trauma/vascular accidents and chorionic villous sampling procedures.[5,6,8-10]

There is evidence of maternal hyperthermia causing OHLS.[3,7,8] A range of defects including limb reduction, central nervous system (CNS) defects, facial dysmorphogenesis, and fetal death has been associated with maternal fever at/above 102°F (38.8 °C) between 4–14 weeks of gestation. Heat induced vascular disruption of the embryo has been implicated in the pathogenesis.[7,8] The extent, duration, and timing of the maternal fever predicts the nature of the anomalies and the most common consequence of gestational hyperthermia appears to be CNS defects. [6] However, patients with OHLS are often born with normal intelligence, so based on this, there is a need to explore maternal hyperthermia as a cause of the syndrome.

Reports of exposure to drugs like Tigan, Benedictine, Imipramine, Diazepam, Chlorpromazine, and Meclizine suggest their involvement, but their effect in the causation of this syndrome has not been proved.[5,11]

There is considerable overlap between the syndromes gathered under the term OLHS, with a marked variability of face and limb anomalies as well as other additional malformations.[6] OLHS was first reported by Rosenthal in 1932 as Aglossia Cogenita.

Hall in 1971 recognised five main categories. The only criteria necessary for inclusion is the occurrence of hypoglossia, with the exception of category Type V, which contains a miscellany of syndromes.[10,13] (Table: 1)

Another classification system was proposed by Chicarilli in 1985 in which the clinical presentation as well as the embryologic origin was taken into consideration.[10,14] He recognised four major classes: Type 1: showing micrognathia, Type 2: based on microglossia as the primary disorder from subtle microglossia to total absence of the tongue, Type 3: presenting with glossopalatine ankylosis, including all intraoral bands that span the intermaxillary space, Type 4: including Möbius and Charlie M syndrome. (Table: 1)

Table 1: Classification of syndromes of oromandibular and limb hypogenesis[15]

Hall (1971)[13]	***Chicarilli (1985)***[14]
Type I: A. Hypoglossia B. Aglossia	**Type I:** *Micrognatia* (mandibular) - Pierre Robin syndrome - Hanhart syndrome
Type II: A. Hypoglossia-hypodactilia B. Hypoglossia-hypomelia (peromelia) C. Hypoglossia-hypodactylomelia	**Type II:** *Microglossia* - Hypoglossia - Hypoglossia-hypodactyly
Type III: A. Glossopalatine ankyloses B. With hypoglossia C. With hypoglossia-hypodactilia D. With hypoglossia-hypomelia E. With hypoglossia-hypodactylomelia	**Type III:** *Dysgnathia* (maxilo-mandibular) - Glossopalatine ankyloses - Glossopalatine ankyloses hypodactyly

Type IV: A. Intraoral band and fusion B. With hypoglossia C. With hypoglossia-hypodactilia D. With hypoglossia-hypomelia E. With hypoglossia-hypo-dactylomelia	**Type IV**: Other - Möbius syndrome - Charlie M syndrome - (Amniotic band syndrome)
Type V: A. Hanhart syndrome B. Charlie M syndrome C. Pierre Robin syndrome D. Möbius syndrome E. Amniotic band syndrome	

Some confusion was addressed by Chicarilli when they modified Hall's earlier 1971 clinically based classification in favour of a clinical–embryological system. However, some cases present with stigmata that bridge two or more syndromes further complicating their diagnosis and classification.[12] Another limitation of the two most frequently used classification for OLHS is they do not recognise glossopalatine ankyloses syndrome as part of the criteria for Charlie M syndrome. Glossopalatine ankyloses is a very rare syndrome where the tongue itself or an intraoral band from the tongue is usually attached to the hard palate, or nasal septum in the case of a cleft palate, or the maxillary alveolar ridge. Less than 30 cases of glossopalatine ankyloses have been reported in the literature so far.

In 2016 Jung *et al.* reported a case with features suggestive of Charlie M syndrome and proposed a revised classification for OLHS.[17] Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature.[15] Grippaudo *et al.* came to the conclusion that glossopalatine ankyloses was an entirely new malformation after describing a case with phenotypical malformations of the face and extremities similar to Charlie M syndrome.

Jung and coworkers suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system. They sub-classified Charlie M syndrome into Type I – no glossopalatine ankyloses and Type II – with glossopalatine ankyloses.

They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities. Amniotic band syndrome that is included in Hall and Chicarilli's classification is not included by Jung. Table 2 illustrates the newer classification of OLHS as proposed by Jung *et al.*

Table 2: Newer classification of former OLHS by Jung et.al: Oromandibular limb hypogenesis malformations (OLHM)[17]

	Type I:	**Type II:** *Dysgnathia with*	**Type III:** *Dysgnathia and glossopalatine ankyloses/intraoral bands of fusion with*	**Type IV:** *Miscellaneous*
A	Hypoglossia/ Aglossia	Hypoglossia/ aglossia	Hypoglossia/ Aglossia	Hanhart syndrome
B	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Möbius syndrome
C				Charlie M syndrome Type I - no glossopalatine ankylosis
D				Charlie M syndrome Type II – glossopalatine ankyloses
E				Robin sequence

In order to correctly classify the different OLHS subtypes a proper phenotypical description of the orofacial and skeletal as well as other associated abnormalities of each syndrome is needed. Current classification systems lack a minimal criteria of absolute clinical features needed to diagnosis each of the OLHS subtypes, further complicating the classification of this syndrome.

The phenotypical description of OLHS subtypes that is available according to current literature will briefly be summerized to illustrate the overlapping features and lack of minimal criteria to classify a OLHS subtype.[16, 17]

Hypoglossia-hypodactylia: also called aglossia-adactylia syndrome, which is a misnomer since the tongue is never completely absent and the term “adactylia” does not convey the variation in limb defects of affected individuals.

1. Mouth:
   a. Mandible
      i. Micro/retrognathia
      ii. Oligodontia
      iii. Absent mandibular incisors with concomitant hypoplasia of the associated alveolar ridge
      iv. Other features
         a) Mild lower lip defect
         b) Microstomia
         c) Intraoral bands
         d) Oral frenula
         e) Oral syngnathia
   b. Tongue:
      i. Varying degree of hypoglossia
      ii. Ankyloglossia
2. Variable limb anomalies
   a. May involve any limb
   b. Distal reduction anomalies
      i. Oligodactyly (absence of some fingers and toes)
      ii. Adactylia (congenital absence of the fingers and toes)

iii.Peromelia (severe congenital malformation of the extremity, including absence of hand and foot)

c. Syndactyly

3. Other associated anomalies

a. Fused labia majora

b. Unilateral renal agenesis

c. Imperforate anus

Glossopalatine and ankylosis syndrome: very rare syndrome with less than 30 cases reported in the literature so far.

i. Tongue itself or an intraoral band from the tongue

a) Usually attached to the hard palate, or nasal septum if cleft palate
b) May adhere to the maxillary alveolar ridge

c) Mildly cleft tongue tip

ii. High-arched or cleft palate

iii. Hypoplastic mandible

iv. Hypodontia principally affects the incisor teeth

v. Ankylosis of the temporomandibular joint

vi. Facial paralysis

Extremely variable limb anomalies

a) Oligodactyly (absence of some fingers and toes)

b) Syndactyly

c) Polydactyly

d) Peromelia (severe congenital malformation of the extremity, including absence of hand and foot)

Table 3: Phenotypical description of Hall Type V, Chicarilli Type IV and Jung Type IV OLHS syndromes[17]

	Orofacial	Skeletal	Other
Charlie M	facial asymmetry hypertelorism, telecanthus short philtrum micrognathia microstomia aglossia, hypoglossia absent teeth cleft palate gingival fibromatosis Jung *et al.* acknowledge glossopalatine ankyloses as part of Charlie M syndrome Type I: no glossopalatine ankyloses Type II: with glossopalatine ankyloses	ectromelia etrodactyly oligodactyly abnormal finger and toenail morphology	macrotia (large ears) may exhibit caracteristics of Poland syndrome
Hanhart	facial asymmetry hypertelorism, telecanthus, short philtrum, micrognathia micostomia, aglossia, hypoglossia, absent teeth cleft lip/palate glossolabial adhesion	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia splenogonodal fusion cryptorchidism brain cysts intellectual disability
Möbius	as for Hanhart CN VII defect (major criteria) CN III, IV, VI, IX, X, XII defects possible external ear abnormalities	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia seizures congenital cardiac lesions
Pierre-Robin	cleft palate glossoptosis micrognathia	sometimes taped fingers, clinodactyly	20-40% isolated, otherwise part of other syndromes like Stickler

4. AIMS AND OBJECTIVES

A three month old male infant presented to our outpatient department with clinical features that straddled more than one syndrome as classified under the OLHS. Given the orofacial and extremity malformations of this case it could be classified as Hall Type IIID or VB and Chicarilli Type IV.

This rare case illustrated the shortcomings of current classification systems and led to the formulation of the research question: “Can the current acknowledged classification systems accurately classify the spectrum of Oromandibular-limb hypogenesis syndrome?”

A modification of the Chicarilli classification that was proposed by Jung *et al*. in 2016 made classification of this particular case possible (Table: 2). However, this proposed classification system is not currently acknowledged or used in the literature.

The aim of this case report was thus to contribute to understanding the difficulty in the classification of these complex malformations with our current acknowledged classification systems and the objectives were to:

- Review the current classification systems to identify the limitations as well as advantages of the different classification systems that are currently available
- Recommend a single system that can accurately classify the majority of the OLHS subtypes

5. ETHICAL CONSIDERATIONS

Approval to present this case report was obtained from the Health Science Research Committee of the University of the Free State (final ethical clearance number: UFS-HSD2018/1151/2901) as well as from the Department of Health Research Data Base (Dr D Motau : Head of DOH Free State). Consent to present this case report was obtained from the infant’s mother and was also approved by the recognised ethics committees.

6. CASE PRESENTATION

Relevant history: A three month old male infant was referred to the Plastic and Reconstructive outpatient department of Universitas hospital in March 2017 for workup of possible oromandibular-limb hypogenesis syndrome.

The infant was born at term via uncomplicated vaginal delivery to a 27 year-old gravida three with no prior miscarriages. The mother was on Atroiza, a combination anti-retroviral drug containing efavirenz/emtricitabine/tenofovir, throughout her pregnancy. Certain drugs have been implicated in the aetiology of OLHS, but no prior cases had exposure to ARV's. She had unremarkable prenatal sonograms and denied any alcohol/drug abuse, or febrile episodes or illnesses during this pregnancy. The infant's parents and other siblings were all normal with no craniofacial and skeletal abnormalities, thus this was most likely a sporadic case.

Main concern of mother was the tongue that was adhered to the hard palate with regurgitation of milk feed through the nose which complicated breast and bottle feeding.

Clinical examination: The infant presented with a normal head circumference and weight for age. The frontal hairline was in a normal position, inspection of the orbits revealed telecanthus (increased distance between the medial canthi of the eyes) and down slanting palpebral fissures. There was a flattened nasal bridge with normal midface height and volume. Bilateral low set ears with a deficiency of the superior thirds and lobbing of the helical rims was also present. (Figure 1)

Oral examination showed a normal upper lip volume and a hypoplastic lower lip with down turned oral commissures. Micrognathia as well as retrognathia was evident with no airway obstruction clinically. Intraoral examination was difficult because of limited mouth opening due to the hypoplastic mandible. The tongue was adhered to the secondary palate with visible clefting of the secondary palate and a collapsed and hypoplastic alveolus on the right. (Figure 2)

Figure 1: Illustrating the orofacial malformations

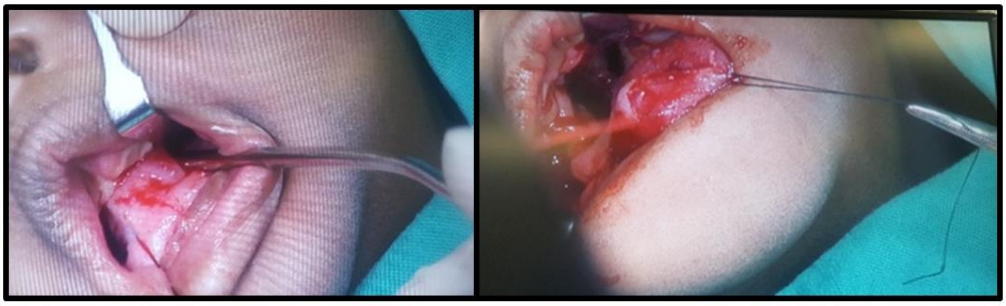

Figure 2: illustrating the intraoral findings of glossopalatine ankylosis

Examination of the trunk and back revealed no obvious pathology with normal male genitalia. The right upper limb showed hypomelia (deficiency of some or all parts of one of more limbs) with deficiency of the nails (anonychia) and fingertips of the second to fourth digits. The left upper limb showed hypomelia of the second to fifth digits with anonychia, patient also had hyponychia of the thumb nail. (Figure 3)

Examination of the lower limbs showed bilateral talipes equinovarus. The left foot had anonychia and hypomelia of the first and second toes, the right foot had anonychia and hypomelia of the first, second and third toes, with an incomplete syndactyly of the first webspace. (Figure 4)

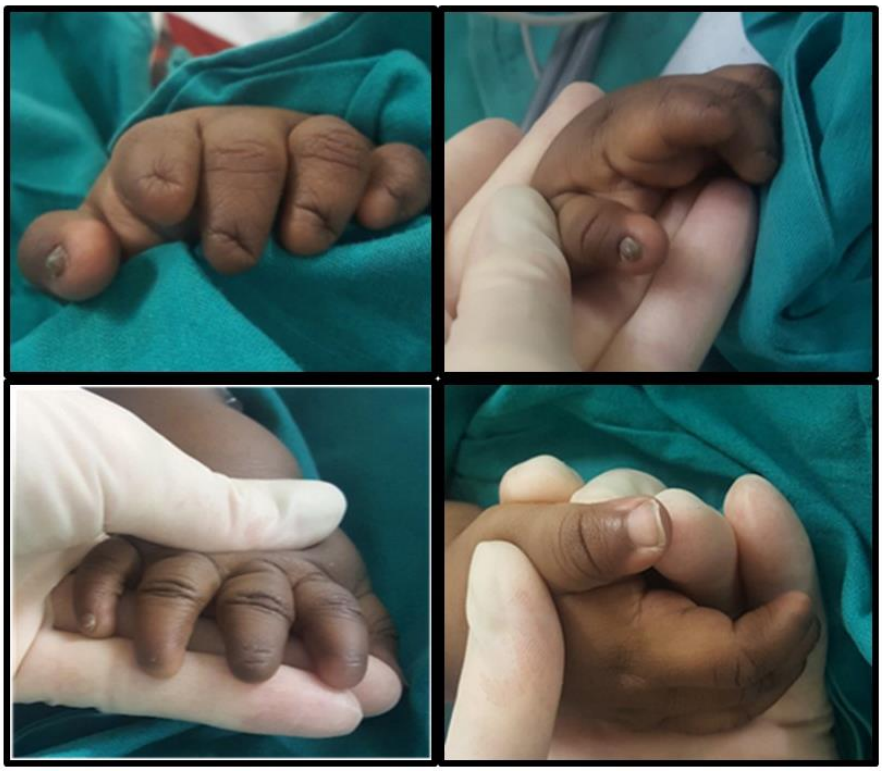

Figure 3: illustrating the upper extremity malformations

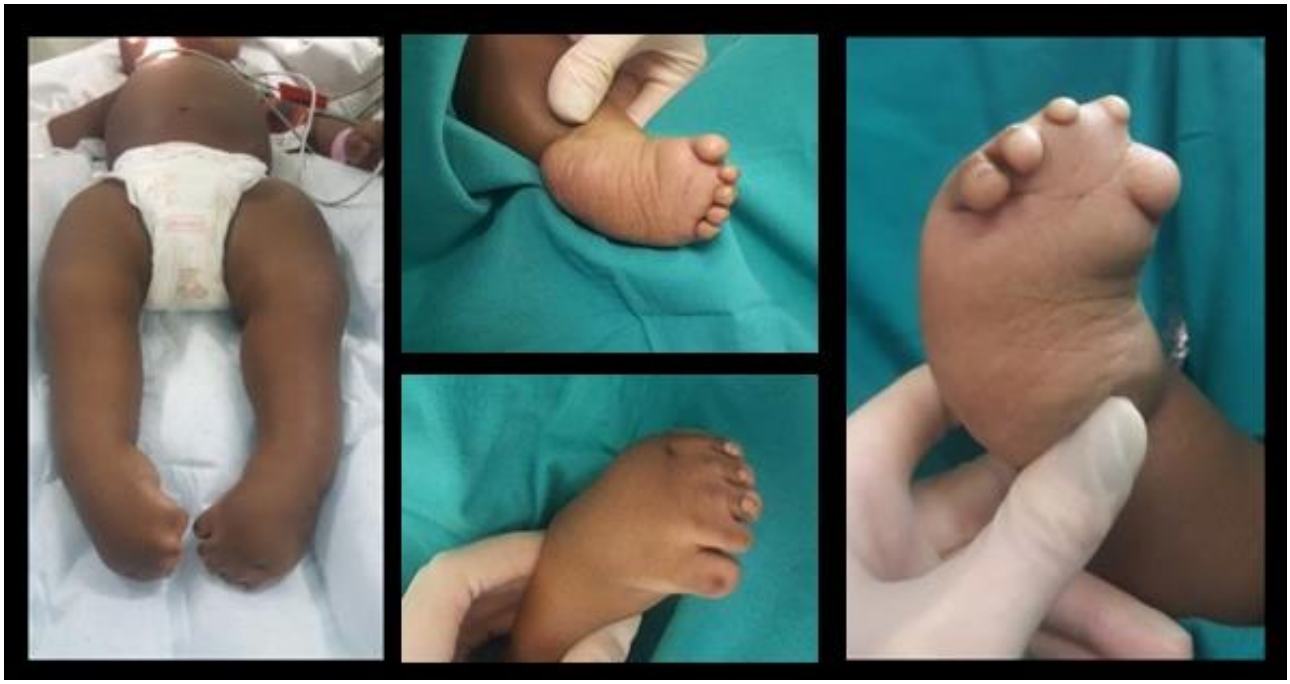

Figure 4: illustrating the lower extremity malformations

Diagnostic investigations: An echocardiography was performed that showed no morphological or functional cardiac defects as well as an abdominal ultrasound that excluded intra-abdominal pathology. Plain x-rays of the cervical spine and chest showed no skeletal abnormalities. X-rays of the hands and feet revealed hypomelia of the second to fifth distal phalanges of the left hand, and hypomelia of the second to fourth distal phalanges of the right hand. Left foot x-rays showed hypomelia of the first and second toe distal phalanges, and the right foot showed hypomelia of the first to third toes distal phalanges, with an incomplete syndactyly of the first web space.

A contrasted computerized tomography of the facial bones and soft tissues showed the following: a midline defect in the hard palate creating a communication between the anterior nasal cavities and the oral cavity. The tongue could not be separated from the anterior hard palate, with hypoplasia of the right alveolar ridge (Figure 5). Hypoplasia and retrusion of the mandible was also evident. Intracranial findings included: dilated lateral ventricles, a cavum velum interposition cyst, midline infratentorial dorsal cyst with slight mass effect on the cerebellar hemispheres. Intracranial findings most likely due to corpus callosum dysgenesis.

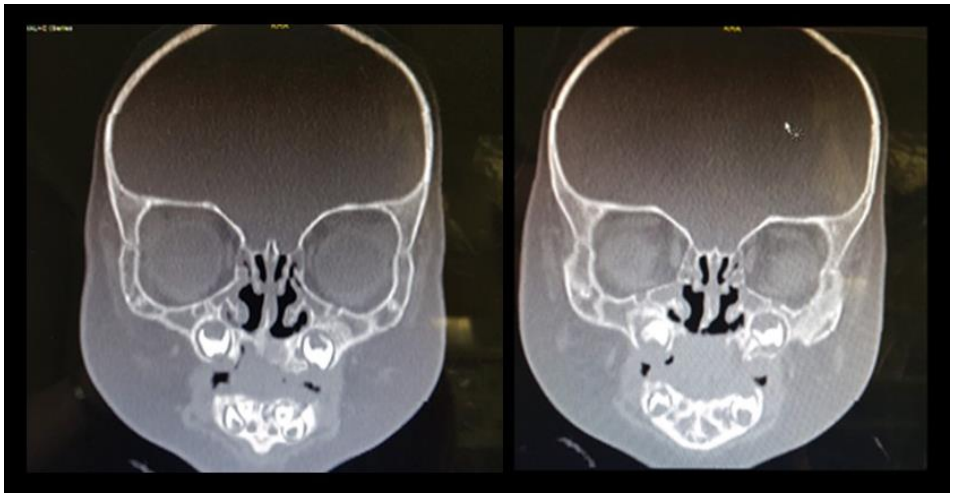

Figure 5: illustrating the CT findings

Management: A multi-disciplinary team approach was followed in the management of this patient. Genetic counselling was done by the genetics team to explain the possible aetiology and pathogenesis as well as the recurrence risk for future pregnancies. No formal genetic testing was done seeing that this was most likely a sporadic case.

The paediatric orthopaedic department managed the clubbed feet with the Ponseti method (manipulative splinting in plaster of Paris casts). Milestones were delayed in terms of crawling and walking and physiotherapy and occupational health is still assisting with rehabilitation.

Our plastic and reconstructive team performed staged surgery for the glossopalatine ankyloses, by releasing the hypoplastic tongue from the hard palate in the first setting, (March 2018). This was followed by repair of the complete secondary palate cleft with a Von Langenbeck palatoplasty to address the hard palate defect and an intravelarveloplasty to repair the soft palate defect, performed in September 2018.

On future follow up speech will be closely monitored for velopharyngeal dysfuction. Orthodontic interventions may be needed in future as well as possible mandibular distraction osteogenesis or mandibular advancement. The fine motor function of the hand will need to monitored, the hypoplastic distal phalanges should theoretically not interfere too much with function. The syndactyly of the right foot first web can be addressed in future for functional and cosmetic purposes.

7. DISCUSSION

As mentioned earlier OLHS in general and particularly the concordant syndromes are very difficult to diagnose due to their overlapping phenotypical features as well as the low incidence rate.[17] These malformations are extremely rare with an incidence of 1:175 000 live births and for Glossopalatine ankylosis syndrome less than 30 cases have been reported in the literature so far.

The literature does not state what the incidence of OLHS is among different ethnic groups, but case reports found on a MEDLINE search are mainly from India, Philippines, Japan, Turkey and South Africa (one Coloured and one African infant).[4,10,12,15,17] No caucasian cases were found during the literature search.

Perks et al reported the only known case of OLHS in South Africa in 2008.[10] It was a neonate that was referred to Tygerberg hospital with features compatible with Type 4A (intraoral bands and fusion), Type 4E (hypoglossia–hypodactylomelia) and also Type 5A (Hanhart syndrome) of Hall's classification. This patient also had features of Types 1, 2 and 3 of Chicarilli classification of OMLH syndromes.

Several attempts have been made to explain the emergence of OLHS, Charlie M syndrome and glossopalatine ankyloses.[15,17] Defects in facial and limb differentiation usually occur during days 28–63 of the embryologic development. By day 32 the upper extremity development begins, it then further differentiates into the arm, forearm and hand at day 37. The hand finally appears differentiated when the digits separate by day 46. Development of the lower extremity is delayed by about one week.[15,17]

The development of glossopalatine ankyloses can currently be explained by two possible theories.[18,19] One theory hypothesizes that persistence of the buccopharyngeal membrane (BPM) results in the appearance of intraoral bands. The BPM develops when the intraembryonic mesoderm does not invade all parts of the intraembryonic disc which results in separation of the stomatodeum entoderm and the foregut ectoderm up to day 26. As result of rapid growth of the pharynx, tongue and facial structures, the tension of the BPM becomes greater which leads to breakdown of this membrane.

The other theory hypothesize the persistence of a sub-glossopalatal membrane or ectopic membranes.[20] Between the sixth and eighth week of the embryonic development these membranes appear and normally disappear when the tongue descends around the ninth week. Membranous fusion between the upper and lower jaw can thus be the result of either the persistence of membranes, failure of the tongue to drop down or both.

In this case report an infant is presented with stigmata that straddle more than one syndrome as classified under the OLHS. The oral and limb deformities included: telecanthus, down turned palpebral fissures, a flat nasal bridge, and both ears were lobbed with constricted upper thirds. The patient also had microstomia with an underdeveloped lower lip as well as micrognathia. Intraoral examination showed

glossopalatine ankyloses, a hypoplastic tongue was fused to the nasal septum with clefting of the secondary palate, with a hypoplastic and collapsed right alveolus. Skeletal malformations included hypomelia of the distal digits of the hands and feet, abnormalities of the finger and toenails as well as bilateral clubbed feet.

Based on these phenotypical findings the patient can be classified as a Hall IIID (glossopalatine ankyloses with hypoglossia-hypomelia) or Hall V (Charlie M syndrome), and a Chicarilli IV (Charlie M syndrome). (Table: 1) Hall and Chicarilli's classification of Charlie M does not include glossopalatine ankyloses so this subtype will have to be classified on the bases of other criteria for Charlie M. (Table 3)

Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature.[15] Grippaudo et al. came to the conclusion that glossopalatine ankyloses was an entirely new malformation after describing a case with phenotypical malformations of the face and extremities similar to Charlie M syndrome.

In 2016 Jung and coworkers reported a case with features suggestive of Charlie M syndrome and proposed a revised classification for OLHS.[17]

They suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system. They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities. Table 2 illustrates the new classification of OLHS as proposed by Jung *et al.*

By using this new proposed classification system the phenotypical findings of our case report will be in keeping with a Type IV D (Charlie M syndrome Type II: with glossopalatine ankyloses) (Table 2).

8. CONCLUSION

There is considerable overlap between the syndromes grouped together under the umbrella of OLHS and there is controversy whether these syndromes are just varying presentations of the spectrum of OLHS. Thus further contributes to the difficulty in classifying this syndrome and its subtypes.

A proper phenotypical description of the orofacial and skeletal as well as other associated abnormalities of each syndrome is needed In order to correctly classify the different OLHS subtypes. Current classification systems (Hall, Chicarilli and Jung) lack a minimal criteria of absolute clinical features needed to diagnosis each of the OLHS subtypes.

Some confusion was addressed by Chicarilli when they modified Hall's earlier 1971 clinically-based classification in favour of a clinical–embryological system. Limitations identified in Chicarilli's classification include a limited description of the extremity abnormalities, only hypodactyly is mentioned and hypomelia and hypodactylomelia is excluded. Another limitation of the two most frequently used classification for OLHS is they do not recognise glossopalatine ankyloses syndrome as part of the criteria for Charlie M syndrome.

Jung *et al.* proposed a revised classification of Chicarilli for OLHS.[17] [15] They suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system, which is definitely an improvement. Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature. Jung et al recognised glossoplataine ankyloses as part of Charlie M syndrome and sub-classified it into Type I – no glossopalatine ankyloses and Type II – with glossopalatine ankyloses.

They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities.

Limitations of Jung's classification also include a limited description of the extremity abnormalities, as in the case of Chicarilli. Amniotic band syndrome that is included in Hall and Chicarilli's classification is not included by Jung, this may limit classification of a small subtype of OLHS. Jung and coworkers proposed to exclude this syndrome since it can only clarify the extremity malformations but not the facial dysmorphology.

Given the orofacial and limb malformations of this case it could be classified as a Hall IIID *or* VB and a Chicarilli Type IV. By using the proposed classification by Jung *et al*. this patient can easily be sub-classified into Type IV D: Charlie M syndrome (Type II) that acknowledge glossopalatine ankyloses as part of the syndrome.

The classification by Jung *et al*. can also be used to sub-classify other OLHS case reports in the literature that was previously difficult to classify using Hall and Chicarilli's systems. The case report by Perks et al. can now be sub-classify as Jung Type IV D.

The Jung classification can be used to sub-classify the majority of OLHS cases, with amniotic band syndrome cases as an exception.

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10. APPENDICES

A) Letter of approval from Health Science Research Ethics Committee

B) Participant information form and Consent form

C) Permission from DOH - NHRD

D) Permission from HOD

E) Copy of the research protocol approved by the HSREC

F) Instructions to authors of the named peer reviewed journal

G) A summary report compiled in the TURNITIN Plagiarism Search Engine

A) Letter of approval from Health Science Research Ethics Committee

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Health Sciences Research Ethics Committee

26-Nov-2018

Dear **Dr Lizanne Small**

Ethics Clearance: **Case report**
Principal Investigator: **Dr Lizanne Small**
Department: **Plastic Surgery Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/1151/2901**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za

B) Participant information form and Consent form

FACULTY HEALTH SCIENCE
DEPARTMENT OF PLASTIC& RECONSTRUCTIVE SURGERY
PO Box 339 (G35), Bloemfontein 9300, SA
Telephone: (051) 4053544 Faks/Fax: (051) 4440875

INFORMATION LETTER:

RE: THE USE OF PATIENT INFORMATION IN A CASE REPORT:

I, Dr L Small, am currently busy with the final year of my studies in Plastic and Reconstructive surgery. As part of my training I need to do research to receive my degree from the University of the Free State.

After my first meeting with you and your child in our outpatient clinic I realized that your child has a very rare birth abnormality. I then went and did some research on his condition and realized that if I can write a case report about your child it will help other doctors with the treatment of children that are suffering from the same condition. A case report is basically a short story that you write about an interesting patient, how you first met the patient, the rare birth abnormalities that was picked up and how it was treated. This story can also use photos of the patient to show the abnormalities that are present and this story can appear in medical magazines to teach other doctors. This information is always treated with respect and no patient's name will appear in a case report.

I would like you to think about the fact that I want use your child's medical records and photos to make such a case report. Your participation is completely voluntary, meaning that nobody can force you to agree. If you feel at any point that you don't want us to continue with this case report you can withdraw your permission, this with not have any negative effect on your child's treatment at Universitas hospital.

Kind regards.

Dr L Small
Universitas hospital, Plastic and Reconstructive surgery
Contact number: 051 405 3544

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Telephone: (051) 4053544 Faks/Fax: (051) 4440875

CONSENT FOR USE OF PATIENT INFORMATION IN CASE STUDY:

I AYANDA NQODI, parent of NQODI, TLHALETO hereby acknowledge that the following information is correct:

- I was informed that my child has a very rare birth abnormality and only 30 of these cases has been reported worldwide
- Dr L Small from the department of Plastic and Reconstructive surgery consulted with me to discuss the possibility to access my child's medical records and use it to write a case report about my child's rare condition
- In this case report my child's identity will be protected, but relevant personal information as well as digital photographs showing these birth abnormalities will be used (this includes photos of my child's face, hands and feet)
- I know that this case report, containing my child's personal information and photos may appear in medical magazines
- I know that the decision to allow my child's information to be used in this case report is completely voluntary
- I can at any point withdraw my consent without any negative impact on the medical management of my child

I hereby give permission for my child's medical records and photos to be used in the above mentioned case report conducted by Dr L Small.

Signed at Bloemfontein on this 15th day of August 2018

* Ayanda Nqodi ..... * .....
(Name and Surname) (Signature)

Witness 1. .....
N BLAKE

Witness 2. .....
S. V AGARWAL

C) Permission from DOH – National Research Data Base

health
Department of Health
FREE STATE PROVINCE

19 November 2018

Dr L Small
Dept. of Plastic Surgery
UFS

Dear Dr L Small

Subject: Oromandibular Limb Hypogenesis syndrome - A rare case illustrating shortcomings of current classification systems

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 29/11/18

Head : Health
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www.fs.gov.za

D) Permission from HOD

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SUPPORTING LETTER TO PERFORM CASE REPORT AS PART OF MMed RESEARCH STUDY

I Prof JF Jooste hereby confirm that Dr L Small is currently a registrar in her final academic year in the Department of Plastic and Reconstructive surgery. In order to obtain her MMed degree from the University of the Free State she needs to perform a research study.

As head of the Plastic and Reconstructive surgery department I hereby give permission that Dr L Small can submit the proposed case report named: "*Oromandibular limb hypogenesis syndrome : A Rare Case Illustrating Shortcomings of current classification systems*" as part of her MMed research study. I will also be her supervisor for this proposed case report.

I trust that you will find this in order.

Kind regards.

.....
Prof JF Jooste
Head of Plastic and Reconstructive surgery
University of the Free State
Bloemfontein
051– 405 3544

E) Copy of research protocol approved by the HSREC

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RESEARCH PROTOCOL

"Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in Plastic and Reconstructive Surgery in the Faculty of Health Sciences at the University of the Free State."

CASE REPORT TITLE

Oromandibular-limb Hypogenesis Syndrome: A Rare Case Illustrating Shortcomings of Current Classification Systems

Researcher: Dr Lizanne Small
Registrar - Plastic and Reconstructive Surgery
Universitas Academic hospital
University of the Free State
Bloemfontein
South Africa

Supervisor: Prof Johannes Frederick Jooste
Head of Department - Plastic and Reconstructive Surgery
Universitas Academic hospital
University of the Free State
Bloemfontein
South Africa

TABLE OF CONTENTS

INTRODUCTION

Oromandibular-limb hypogenesis syndromes (OLHS) (OMIM 103300) represent a spectrum of congenital dysmorphic complexes that are characterized by abnormalities of the oral cavity and mandible (including hypoglossia, aglossia, micrognathia, glossopalatine ankylosis, cleft palate, and gingival anomalies) as well as severe asymmetric limb defects (primarily involving distal segments).[1-3]

These malformations are extremely rare with an incidence of 1:175 000 live births and only a few cases have been reported in the literature to date.[1,3]

Several attempts have been made to explain the emergence of OLHS and the interaction of both genetic and environmental factors in the OLHS aetiology are acknowledged in the literature.[3] The majority of cases reported in the literature are sporadic but few have intra-familial history.[4]

Inheritance of mutated *Msx2,* a homeobox gene that is associated with craniofacial and limb malformation, has been proposed but till date, no genetic mutation or chromosomal abnormalities have been identified for this syndrome.[4-7]

Environmental factors likely to be the aetiology are maternal hyperthermia, maternal exposure to radiation and teratogenic drugs, intrauterine trauma/vascular accidents and chorionic villous sampling procedures.[5,6,8-10]

There is evidence of maternal hyperthermia causing OHLS.[3,7,8] A range of defects including limb reduction, central nervous system (CNS) defects, facial dysmorphogenesis, and fetal death has been associated with maternal fever at/above 102°F (38.8 °C) between 4–14 weeks of gestation. Heat induced vascular disruption of the embryo has been implicated in the pathogenesis.[7,8] The extent, duration, and timing of the maternal fever predicts the nature of the anomalies and the most common consequence of gestational hyperthermia appears to be CNS defects. [6] However, patients with OHLS are often born with normal intelligence, so based on this, there is a need to explore maternal hyperthermia as a cause of the syndrome.

Reports of exposure to drugs like Tigan, Benedictine, Imipramine, Diazepam, Chlorpromazine, and Meclizine suggest their involvement, but their effect in the causation of this syndrome has not been proved.[5,11]

There is considerable overlap between the syndromes gathered under the term OLHS, with a marked variability of face and limb anomalies as well as other additional malformations.[6] OLHS was first reported by Rosenthal in 1932 as Aglossia Cogenita.

Hall in 1971 recognised five main categories. The only criteria necessary for inclusion is the occurrence of hypoglossia, with the exception of category Type V, which contains a miscellany of syndromes.[10,13] (Table: 1)

Another classification system was proposed by Chicarilli in 1985 in which the clinical presentation as well as the embryologic origin was taken into consideration.[10,14] He recognised four major classes: Type 1 showing micrognathia, Type 2 based on microglossia as the primary disorder from subtle microglossia to total absence of the tongue, Type 3 presenting with glossopalatine ankylosis, including all intraoral bands that span the intermaxillary space, Type 4 including Möbius and Charlie M syndrome. (Table: 1)

Table 1: Classification of syndromes of oromandibular and limb hypogenesis[15]

Hall (1971)[13]	***Chicarilli (1985)***[14]
Type I: C. Hypoglossia D. Aglossia	**Type I**: *Micrognatia* (mandibular) - Pierre Robin syndrome - Hanhart syndrome
Type II: D. Hypoglossia-hypodactilia E. Hypoglossia-hypomelia (peromelia) F. Hypoglossia-hypodactylomelia	**Type II:** *Microglossia* - Hypoglossia - Hypoglossia-hypodactyly
Type III: F. Glossopalatine ankyloses G. With hypoglossia H. With hypoglossia-hypodactilia I. With hypoglossia-hypomelia J. With hypoglossia-hypodactylomelia	**Type III:** *Dysgnathia* (maxilo-mandibular) - Glossopalatine ankyloses - Glossopalatine ankyloses hypodactyly

Type IV: F. Intraoral band and fusion G. With hypoglossia H. With hypoglossia-hypodactilia I. With hypoglossia-hypomelia J. With hypoglossia-hypo-dactylomelia	**Type IV:** Other - Möbius syndrome - Charlie M syndrome - (Amniotic band syndrome)
Type V: F. Hanhart syndrome G. Charlie M syndrome H. Pierre Robin syndrome I. Möbius syndrome J. Amniotic band syndrome	

Some confusion was addressed by Chicarilli when they modified Hall's earlier 1971 clinically based classification in favour of a clinical–embryological system. However, some case present with stigmata that bridge two or more syndromes further complicating their diagnosis and classification.[12] Another limitation of the two most frequently used classification for OLHS is they do not recognise glossopalatine ankyloses syndrome as part of the criteria for Charlie M syndrome. Glossopalatine ankyloses is a very rare syndrome where the tongue itself or an intraoral band from the tongue is usually attached to the hard palate, or nasal septum in the case of a cleft palate, or the maxillary alveolar ridge. Less than 30 cases of glossopalatine ankyloses have been reported in the literature so far.

In 2016 Jung *et al.* reported a case with features suggestive of Charlie M syndrome and proposed a revised classification for OLHS.[17] Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature.[15] Grippaudo *et al.* came to the conclusion that glossopalatine ankyloses was an entirely new malformation after describing a case with phenotypical malformations of the face and extremities similar to Charlie M syndrome.

Jung *et al*. suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies

in one classification system. They sub-classified Charlie M syndrome into Type I – no glossopalatine ankyloses and Type II – with glossopalatine ankyloses.

They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities. Amniotic band syndrome that is included in Hall and Chicarilli's classification is not included by Jung. Table 2 illustrates the newer classification of OLHS as proposed by Jung *et al.*

Table 2: New classification of former OLHS by Jung et.al: Oromandibular limb hypogenesis malformations (OLHM)[17]

	Type I:	**Type II:** *Dysgnathia with*	**Type III:** *Dysgnathia and glossopalatine ankyloses/intraoral bands of fusion with*	**Type IV:** *Miscellaneous*
A	Hypoglossia/ Aglossia	Hypoglossia/ aglossia	Hypoglossia/ Aglossia	Hanhart syndrome
B	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Möbius syndrome
C				Charlie M syndrome Type I - no glossopalatine ankylosis
D				Charlie M syndrome Type II – glossopalatine ankyloses
E				Robin sequence

In order to correctly classify the different OLHS subtypes a proper phenotypical description of the orofacial and skeletal as well as other associated abnormalities of each syndrome is needed. Current classification systems lack a minimal criteria of absolute clinical features needed to diagnosis each of the OLHS subtypes.

The phenotypical description of OLHS subtypes that is available according to current literature will briefly be summerized to illustrate the overlapping features and lack of minimal criteria to classify a OLHS subtype.[16, 17]

Hypoglossia-hypodactylia: also called aglossia-adactylia syndrome, which is a misnomer since the tongue is never completely absent and the term “adactylia” does not convey the variation in limb defects of affected individuals.

1. Mouth:
   a. Mandible
      i. Micro/retrognathia
      ii. Oligodontia
      iii. Absent mandibular incisors with concomitant hypoplasia of the associated alveolar ridge
      iv. Other features
         a) Mild lower lip defect
         b) Microstomia
         c) Intraoral bands
         d) Oral frenula
         e) Oral syngnathia
   b. Tongue:
      i. Varying degree of hypoglossia
      ii. Ankyloglossia
2. Variable limb anomalies
   a. May involve any limb
   b. Distal reduction anomalies
      i. Oligodactyly (absence of some fingers and toes)
      ii. Adactylia (congenital absence of the fingers and toes)
      iii.Peromelia (severe congenital malformation of the extremity, including

absence of hand and foot)

c. Syndactyly

3. Other associated anomalies

a. Fused labia majora

b. Unilateral renal agenesis

c. Imperforate anus

Glossopalatine and ankylosis syndrome*:* very rare syndrome with less than 30 cases reported in the literature so far.

i. Tongue itself or an intraoral band from the tongue

c) Usually attached to the hard palate, or nasal septum if cleft palate
d) May adhere to the maxillary alveolar ridge

c) Mildly cleft tongue tip

ii. High-arched or cleft palate

iii. Hypoplastic mandible

iv. Hypodontia principally affects the incisor teeth

v. Ankylosis of the temporomandibular joint

vi. Facial paralysis

Extremely variable limb anomalies

b) Oligodactyly (absence of some fingers and toes)

b) Syndactyly

c) Polydactyly

d) Peromelia (severe congenital malformation of the extremity, including absence of hand and foot)

Table 3: Phenotypical description of Hall Type V, Chicarilli Type IV and Jung Type IV OLHS syndromes[17]

	Orofacial	Skeletal	Other
Charlie M	facial asymmetry hypertelorism, telecanthus short philtrum micrognathia microstomia aglossia, hypoglossia absent teeth cleft palate gingival fibromatosis *Jung et al.* acknowledge glossopalatine ankyloses as part of Charlie M syndrome Type I: no glossopalatine ankyloses Type II: with glossopalatine ankyloses	ectromelia etrodactyly oligodactyly abnormal finger and toenail morphology	macrotia (large ears) may exhibit caracteristics of Poland syndrome
Hanhart	facial asymmetry hypertelorism, telecanthus, short philtrum, micrognathia micostomia, aglossia, hypoglossia, absent teeth cleft lip/palate glossolabial adhesion	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia splenogonodal fusion cryptorchidism brain cysts intellectual disability
Möbius	as for Hanhart CN VII defect (major criteria) CN III, IV, VI, IX, X, XII defects possible external ear abnormalities	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia seizures congenital cardiac lesions
Pierre-Robin	cleft palate glossoptosis micrognathia	sometimes taped fingers, clinodactyly	20-40% isolated, otherwise part of other syndromes like Stickler

RESEARCH QUESTION

A three month old male infant presented to our outpatient department with clinical features that straddled more than one syndrome as classified under the OLHS. Given the orofacial and extremity malformations of this case it could be classified as Hall Type IIID or VB and Chicarilli Type IV.

This rare case illustrated the shortcomings of current acknowledged classification systems and led to the formulation of the research question: “Can the current acknowledged classification systems accurately classify the spectrum of Oromandibular-limb hypogenesis syndrome and its subtypes?”

The challenge in classifying this case of OLHS resulted in an in depth literature search for any other proposed classification systems that could address the shortcomings of the classification systems proposed by Hall in 1971 and Chicarilli in 1985. A modification of the Chicarilli classification that was proposed by Jung *et al*. in 2016 made classification of this particular case possible (Table: 2). However, this proposed classification system is not currently acknowledged or used in the literature.

AIMS AND OBJECTIVES

The aim of this case report was thus to contribute to understanding the difficulty in the classification of these complex malformations with our current acknowledged classification systems and the he objectives were to:

- Review the current classification systems to identify the limitations as well as advantages of the different classification systems that are currently available
- Recommend a single system that can accurately classify the majority of the OLHS subtypes

METHODOLOGY

In order to answer the research question a rare case that had presented to our outpatient clinic will be discussed in the form of a case report.

CASE PRESENTATION

Relevant history: A three month old male infant was referred to the Plastic and Reconstructive outpatient department of Universitas hospital in March 2017 for workup of possible oromandibular-limb hypogenesis syndrome.

The infant was born at term via uncomplicated vaginal delivery to a 27 year-old gravida three with no prior miscarriages. The mother was on Atroiza, a combination anti-retroviral drug containing efavirenz/emtricitabine/tenofovir, throughout her pregnancy. She had unremarkable prenatal sonograms and denied any alcohol/drug abuse, or febrile episodes or illnesses during this pregnancy. The infant's parents and other siblings were all normal with no craniofacial and skeletal abnormalities.

Main concern of mother was the tongue that was adhered to the hard palate with regurgitation of milk feed through the nose which complicated breast and bottle feeding.

Clinical examination: The infant presented with a normal head circumference and weight for age. The frontal hairline was in a normal position, inspection of the orbits revealed telecanthus (increased distance between the medial canthi of the eyes) and down slanting palpebral fissures. There was a flattened nasal bridge with normal midface height and volume. Bilateral low set ears with a deficiency of the superior thirds and lobbing of the helical rims was also present. (Figure 1)

Oral examination showed a normal upper lip volume and a hypoplastic lower lip with down turned oral commissures. Micrognathia as well as retrognathia was evident with no airway obstruction clinically. Intraoral examination was difficult because of limited mouth opening due to the hypoplastic mandible. The tongue was adhered to the secondary palate with visible clefting of the secondary palate and a collapsed and hypoplastic alveolus on the right. (Figure 2)

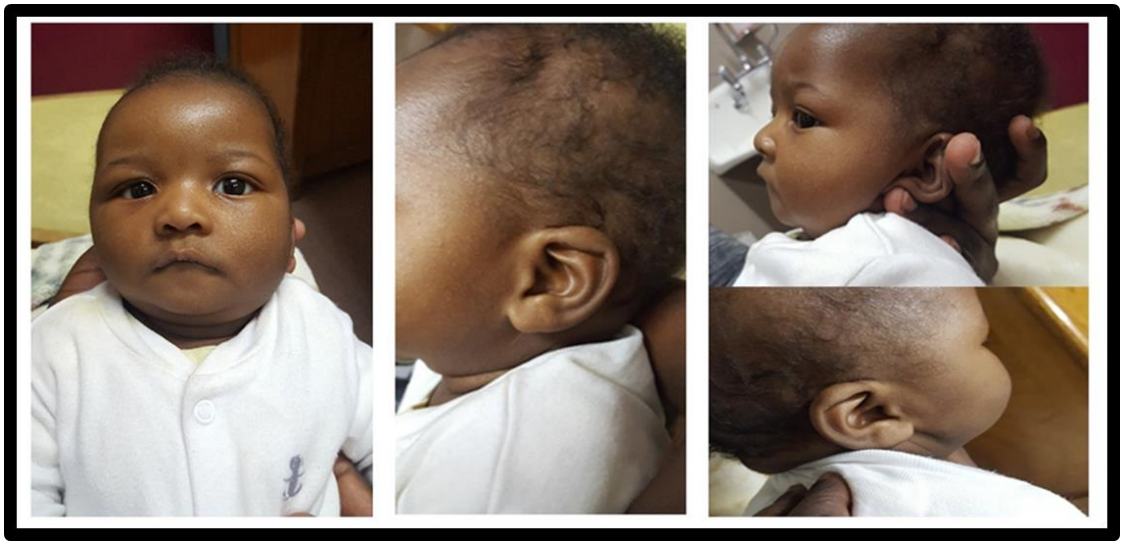

Figure 1: Illustrating the orofacial malformations

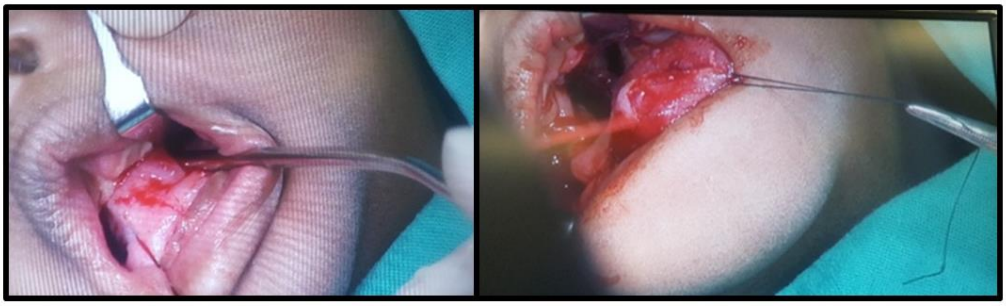

Figure 2: illustrating the intraoral findings of glossopalatine ankylosis

Examination of the trunk and back revealed no obvious pathology with normal male genitalia. The right upper limb showed hypomelia (deficiency of some or all parts of one of more limbs) with deficiency of the nails (anonychia) and fingertips of the second to fourth digits. The left upper limb showed hypomelia of the second to fifth digits with anonychia, patient also had hyponychia of the thumb nail. (Figure 3)

Examination of the lower limbs showed bilateral talipes equinovarus. The left foot had anonychia and hypomelia of the first and second toes, the right foot had anonychia and hypomelia of the first, second and third toes, with an incomplete syndactyly of the first webspace. (Figure 4)

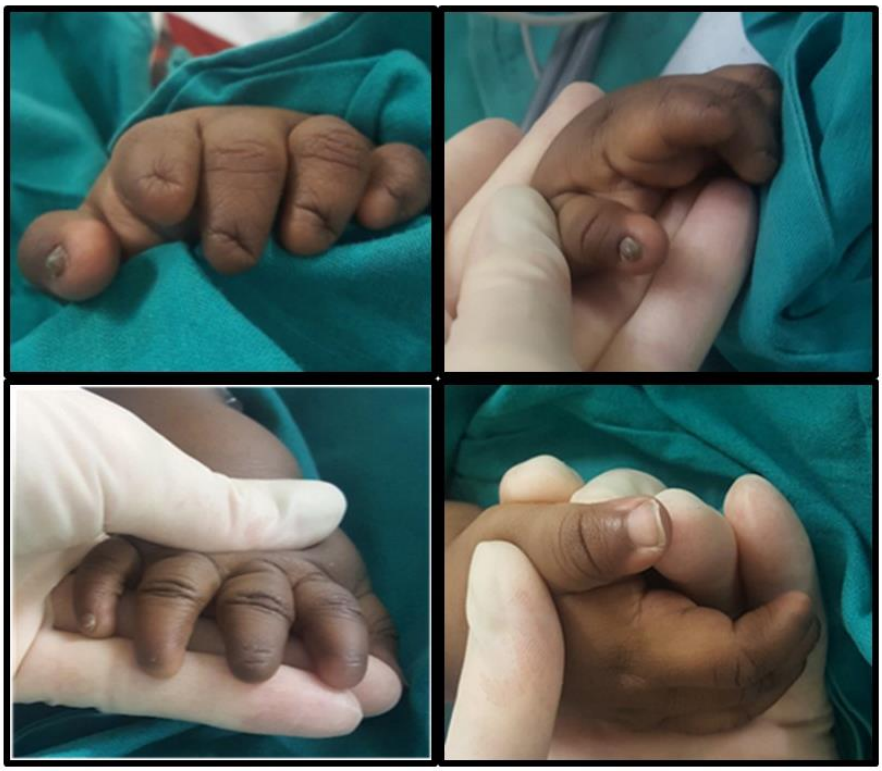

Figure 3: illustrating the upper extremity malformations

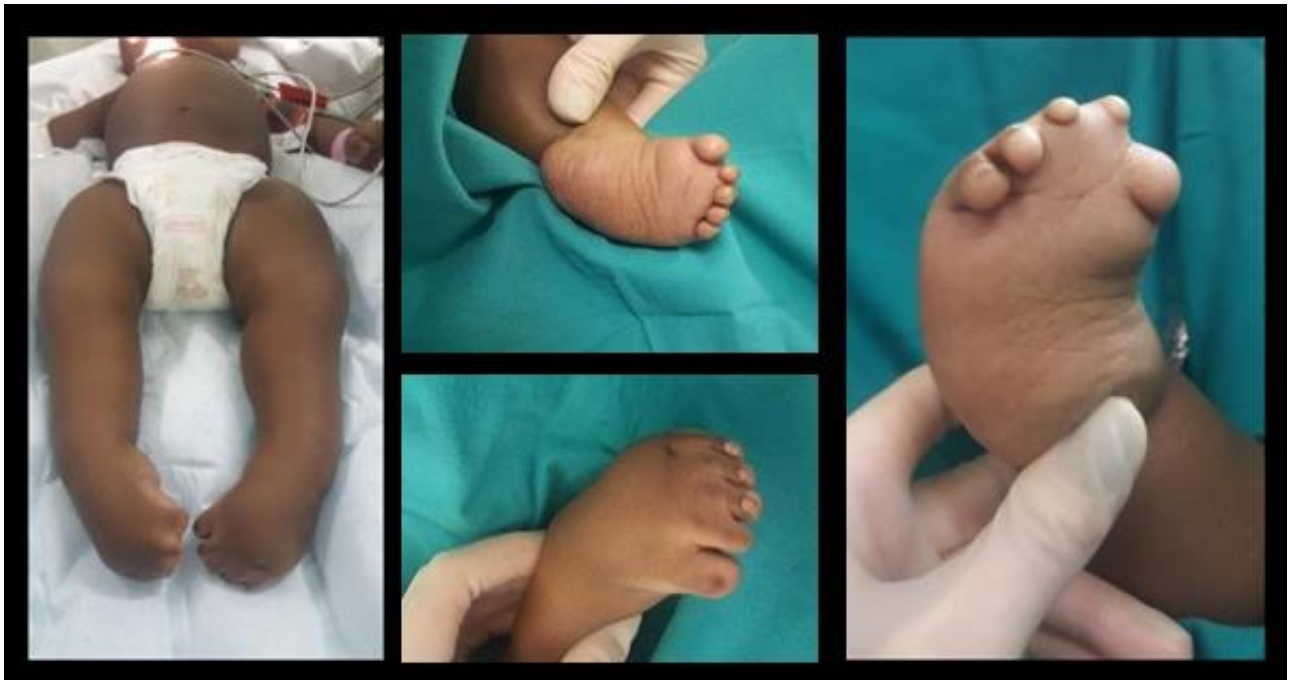

Figure 4: illustrating the lower extremity malformations

Diagnostic investigations: An echocardiography was performed that showed no morphological or functional cardiac defects as well as an abdominal ultrasound that excluded intra-abdominal pathology. Plain x-rays of the cervical spine and chest showed no skeletal abnormalities. X-rays of the hands and feet revealed hypomelia of the second to fifth distal phalanges of the left hand, and hypomelia of the second to fourth distal phalanges of the right hand. Left foot x-rays showed hypomelia of the first and second toe distal phalanges, and the right foot showed hypomelia of the first to third toes distal phalanges, with an incomplete syndactyly of the first web space.

A contrasted computerized tomography of the facial bones and soft tissues showed the following: a midline defect in the hard palate creating a communication between the anterior nasal cavities and the oral cavity. The tongue could not be separated from the anterior hard palate, with hypoplasia of the right alveolar ridge (Figure 5). Hypoplasia and retrusion of the mandible was also evident. Intracranial findings included: dilated lateral ventricles, a cavum velum interposition cyst, midline infratentorial dorsal cyst with slight mass effect on the cerebellar hemispheres. Intracranial findings most likely due to corpus callosum dysgenesis.

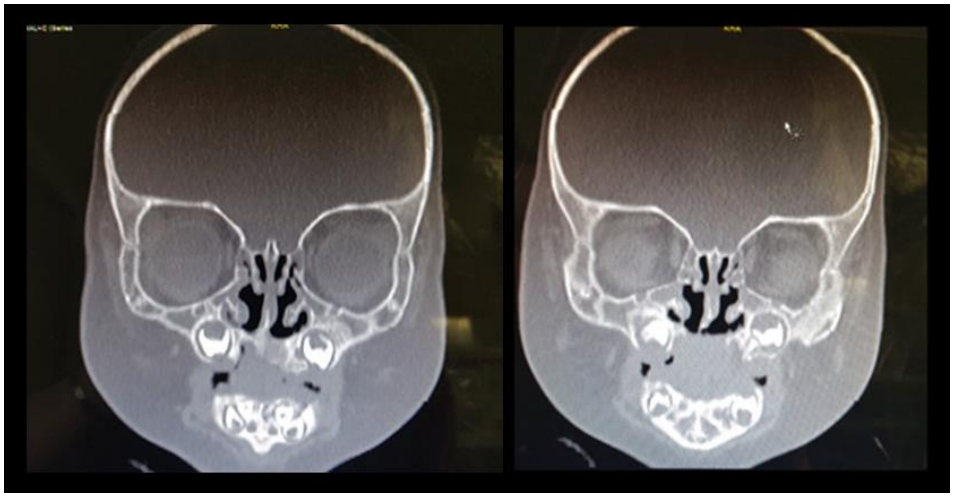

Figure 5: illustrating the CT findings

Management: A multi-disciplinary team approach was followed in the management of this patient. Genetic counselling was done by the genetics team to explain the possible aetiology and pathogenesis as well as the recurrence risk for future pregnancies. No formal genetic testing was done seeing that this was most likely a sporadic case.

The paediatric orthopaedic department managed the clubbed feet with the Ponseti method (manipulative splinting in plaster of Paris casts). Milestones were delayed in terms of crawling and walking and physiotherapy and occupational health is assisting with rehabilitation.

Our plastic and reconstructive team performed staged surgery for the glossopalatine ankyloses, by releasing the hypoplastic tongue from the hard palate in the first setting, (March 2018). This was followed by repair of the complete secondary palate cleft with a Von Langenbeck palatoplasty to address the hard palate defect and an intravelarveloplasty to repair the soft palate defect, performed in September 2018.

On future follow up speech will be closely monitored for velopharyngeal dysfuction. Orthodontic interventions may be needed in future as well as possible mandibular distraction osteogenesis or mandibular advancement. The fine motor function of the hand will need to monitored, the hypoplastic distal phalanges should theoretically not interfere too much with function. The syndactyly of the right foot first web can be addressed in future for functional and cosmetic purposes.

ANALYSIS OF DATA FROM CASE PRESENTATION

As mentioned earlier OLHS in general and particularly the concordant syndromes are very difficult to diagnose due to their overlapping phenotypical features as well as the low incidence rate.[17] These malformations are extremely rare with an incidence of 1:175 000 live births and for *Glossopalatine ankylosis syndrome* less than 30 cases have been reported in the literature so far.

The literature does not state what the incidence of OLHS is among different ethnic groups, but case reports found on a MEDLINE search are mainly from India, Philippines, Japan, Turkey and South Africa (one Coloured and one African infant).[4,10,12,15,17] No caucasian cases were found during the literature search.

Perks et al reported the only known case of OLHS in South Africa in 2008.[10] It was a neonate that was referred to Tygerberg hospital with features compatible with Type 4A (intraoral bands and fusion), Type 4E (hypoglossia–hypodactylomelia) and also Type 5A (Hanhart syndrome) of Hall's classification. This patient also had features of Types 1, 2 and 3 of Chicarilli classification of OMLH syndromes.

Several attempts have been made to explain the emergence of OLHS, Charlie M syndrome and glossopalatine ankyloses.[15,17] Defects in facial and limb differentiation usually occur during days 28–63 of the embryologic development. By day 32 the upper extremity development begins, it then further differentiates into the arm, forearm and hand at day 37. The hand finally appears differentiated when the digits separate by day 46. Development of the lower extremity is delayed by about one week.[15,17]

The development of glossopalatine ankyloses can currently be explained by two possible theories.[18,19] One theory hypothesizes that persistence of the buccopharyngeal membrane (BPM) results in the appearance of intraoral bands. The BPM develops when the intraembryonic mesoderm does not invade all parts of the intraembryonic disc which results in separation of the stomatodeum entoderm and the foregut ectoderm up to day 26. As result of rapid growth of the pharynx, tongue and facial structures, the tension of the BPM becomes greater which leads to breakdown of this membrane.

The other theory hypothesize the persistence of a sub-glossopalatal membrane or ectopic membranes.[20] Between the sixth and eighth week of the embryonic development these membranes appear and normally disappear when the tongue descends around the ninth week. Membranous fusion between the upper and lower jaw can thus be the result of either the persistence of membranes, failure of the tongue to drop down or both.

In this case report an infant is presented with stigmata that straddle more than one syndrome as classified under the OLHS. The oral and limb deformities included: telecanthus, down turned palpebral fissures, a flat nasal bridge, and both ears were lobbed with constricted upper thirds. The patient also had microstomia with an underdeveloped lower lip as well as micrognathia. Intraoral examination showed

glossopalatine ankyloses, a hypoplastic tongue was fused to the nasal septum with clefting of the secondary palate, with a hypoplastic and collapsed right alveolus. Skeletal malformations included hypomelia of the distal digits of the hands and feet, abnormalities of the finger and toenails as well as bilateral clubbed feet.

Based on these phenotypical findings the patient can be classified as a Hall IIIC (glossopalatine ankyloses with hypoglossia-hypomelia) or Hall V (Charlie M syndrome), and a Chicarilli III or IV. (Table: 1) Hall and Chicarilli's classification of Charlie M does not include glossopalatine ankyloses so this subtype will have to be classified on the bases of other criteria for Charlie M. (Table 3)

Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature.[15] Grippaudo *et al.* came to the conclusion that glossopalatine ankyloses was an entirely new malformation after describing a case with phenotypical malformations of the face and extremities similar to Charlie M syndrome.

In 2016 Jung *et al.* reported a case with features suggestive of Charlie M syndrome and proposed a revised classification for OLHS.[17]

They suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system. They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities. Table 2 illustrates the new classification of OLHS as proposed by Jung *et al.*

By using this new proposed classification system the phenotypical findings of our case report will be in keeping with a Type IV D (Charlie M syndrome Type II with glossopalatine ankyloses) (Table 2).

INPLEMENTATION OF FINDINGS

There is considerable overlap between the syndromes grouped together under the umbrella of OLHS and there is controversy whether these syndromes are just varying presentations of the spectrum of OLHS. Thus further contributes to the difficulty in classifying this syndrome and its subtypes.

A proper phenotypical description of the orofacial and skeletal as well as other associated abnormalities of each syndrome is needed In order to correctly classify the different OLHS subtypes. Current classification systems (Hall, Chicarilli and Jung) lack a minimal criteria of absolute clinical features needed to diagnosis each of the OLHS subtypes.

Some confusion was addressed by Chicarilli when they modified Hall's earlier 1971 clinically-based classification in favour of a clinical–embryological system. Limitations identified in Chicarilli's classification include a limited description of the extremity abnormalities, only hypodactyly is mentioned and hypomelia and hypodactylomelia is excluded. Another limitation of the two most frequently used classification for OLHS is they do not recognise glossopalatine ankyloses syndrome as part of the criteria for Charlie M syndrome. Glossopalatine ankyloses is a very rare syndrome where the tongue itself or an intraoral band from the tongue is usually attached to the hard palate, or nasal septum in the case of a cleft palate, or the maxillary alveolar ridge. Less than 30 cases of glossopalatine ankyloses have been reported in the literature so far.

Jung *et al.* proposed a revised classification of Chicarilli for OLHS.[17] [15] They suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system, which is definitely an improvement. Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature. They sub-classified Charlie M syndrome into Type I – no glossopalatine ankyloses and Type II – with glossopalatine ankyloses.

They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities.

Limitations of Jung's classification also include a limited description of the extremity abnormalities, as in the case of Chicarilli. Amniotic band syndrome that is included in Hall and Chicarilli's classification is not included by Jung, this may limit classification of a small subtype of OLHS.

Given the orofacial and limb malformations of this case it could be classified as a Hall IIID *or* VB and a Chicarilli type IV. By using the proposed classification by Jung et al this patient can easily be sub-classified into Type IV D: Charlie M syndrome (Type II) that acknowledge glossopalatine ankyloses as part of the syndrome.

The classification by Jung et al can also be used to sub-classify other OLHS case reports in the literature that was previously difficult to classify using Hall and Chicarilli's systems. The case report by Perks et al. can now be sub-classify as Jung Type IV D.

The Jung classification can be used to sub-classify the majority of OLHS cases, with amniotic band syndrome cases as an exception.

TIME SCHEDULE

The patient that will be used in the case report presented to our outpatient clinic in August 2017. Further diagnostic investigations were performed to assist with the workup that took another month. The initial surgery was scheduled and performed in February 2018 to address the glossopalatine ankyloses. After the surgery it was decided that the second stage of the surgery will be performed in September 2018 to repair the cleft palate.

During the management of this infant it became clear that this was a rare case of OLHS and the decision was made to do an in depth literature study that took about two months to complete. The literature review revealed the difficulty in classifying this

syndrome and highlighted the shortcoming of current classification systems. It was decided that this may be an interesting case report.

Permission to write up this case report will be obtained from my Head of Department, Prof JF Jooste. The parents of the infant will be contacted and an information letter handed out to explain what a case report entails. Informed consent will be obtained to use the clinical information of the infant as well as digital photos and diagnostic imaging, this will take two weeks to complete.

A protocol will then written that will take about two months. The protocol will have to be uploaded onto RIMS and submitted to HSREC in September 2018. Conditional Ethics approval will hopefully be obtained in October 2018 and the Protocol will be submitted to NHRD for final approval, which will be followed by final HSREC approval, provisional date is end of November 2018.

A publishable manuscript will be submitted after final Ethical clearance hopefully beginning of December 2018 that will take about two weeks.

BUDGET

The budget to write up this case report will be kept to a minimum, the only funds payable by the researcher will be for printing of the necessary documentation that was estimated to be about five hundred rand.

The parents' consent to participate in this case report will be completely voluntary with no financial gain.

ETHICAL ASPECTS

ETHICS COMMITTEE

The proposed protocol needs to be submitted onto RIMS (Research Information Management System) for assessment and conditional ethical approval by the HSREC (Health Sciences Research Ethics Committee) of the University of the Free State.

ETHICAL CONDUCT

The parents of this case will need to be informed that participation is completely voluntary with no financial gain. The management of their child will not be negatively influenced if they do not agree to participate. The identity of their child's face will be revealed in the digital photographs, but all data will be treated with confidentiality and respect.

INFORMED CONSENT

Written informed consent for participation in the study will be obtained voluntarily from the parents of this infant seeing that he is still a minor. The information must be sufficient and understandable to enable them to make an informed decision about their participation. The parents may not be blackmailed into participation, for example by implying that health care will be withheld from their child if they do not participate in the research. Patients who do not want to participate must be assured that they will not be disadvantaged because of this. They must be aware that no financial remuneration will be given for participation in the study. Information obtained will be treated as confidential or, where possible, anonymous.

PERMISSION FROM APPROPRIATE AUTHORITIES

The appropriate authorities will be consulted to give permission for the case report to be conducted, which includes:

- Informed consent from parents of the child to use the clinical data as part of a case report
- Permission from my Head of Department, Prof JF Jooste
- Conditional Ethics Approval from the HSREC of the University of the Free State
- Approval from the National Department of Health – NHRD (National Health Research Data Base)
- Final Ethics approval from HSREC

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APPENDICES

- INFORMATION LETTER TO PARENTS
- INFORMED CONSENT FROM PARENTS OF CHILD
- PERMISSION FORM HOD PLASTIC AND RECONSTRUCTIVE SURGERY TO PERFORM THE CASE REPORT
- COVER LETTER TO HSREC UNVERSITY OF THE FREE STATE

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PO Box 339 (G35), Bloemfontein 9300, SA
Telephone: (051) 4053544 Faks/Fax: (051) 4440875

INFORMATION LETTER:

RE: THE USE OF PATIENT INFORMATION IN A CASE REPORT:

I, Dr L Small, am currently busy with the final year of my studies in Plastic and Reconstructive surgery. As part of my training I need to do research to receive my degree from the University of the Free State.

After my first meeting with you and your child in our outpatient clinic I realized that your child has a very rare birth abnormality. I then went and did some research on his condition and realized that if I can write a case report about your child it will help other doctors with the treatment of children that are suffering from the same condition. A case report is basically a short story that you write about an interesting patient, how you first met the patient, the rare birth abnormalities that was picked up and how it was treated. This story can also use photos of the patient to show the abnormalities that are present and this story can appear in medical magazines to teach other doctors. This information is always treated with respect and no patient's name will appear in a case report.

I would like you to think about the fact that I want use your child's medical records and photos to make such a case report. Your participation is completely voluntary, meaning that nobody can force you to agree. If you feel at any point that you don't want us to continue with this case report you can withdraw your permission, this with not have any negative effect on your child's treatment at Universitas hospital.

Kind regards.

Dr L Small
Universitas hospital, Plastic and Reconstructive surgery
Contact number: 051 405 3544

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CONSENT FOR USE OF PATIENT INFORMATION IN CASE STUDY:

I ……., parent of ……,
hereby acknowledge that the following information is correct:

- I was informed that my child has a very rare birth abnormality and only 30 of these cases has been reported worldwide
- Dr L Small from the department of Plastic and Reconstructive surgery consulted with me to discuss the possibility to access my child's medical records and use it to write a case report about my child's rare condition
- In this case report my child's identity will protected, but relevant personal information as well as digital photographs showing these birth abnormalities will be used
- I know that this case report, containing my child's personal information and photos may appear in medical magazines
- I know that the decision to allow my child's information to be used in this case report is completely voluntary
- I can at any point withdraw my consent without any negative impact on the medical management of my child

I hereby give permission for my child's medical records and photos to be used in the above mentioned case report conducted by Dr L Small.

Signed at …… on this …… day of …… 2018

…… ……
(Name and Surname) (Signature)

Witness 1. ……

……

Witness 2. …….

……

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SUPPORTING LETTER TO PERFORM CASE REPORT AS PART OF MMed RESEARCH STUDY

I Prof JF Jooste hereby confirm that Dr L Small is currently a registrar in her final academic year in the Department of Plastic and Reconstructive surgery. In order to obtain her MMed degree from the University of the Free State she needs to perform a research study.

As head of the Plastic and Reconstructive surgery department I hereby give permission that Dr L Small can submit the proposed case report named: "*Oromandibular limb hypogenesis syndrome : A Rare Case Illustrating Shortcomings of current classification systems"* as part of her MMed research study. I will also be her supervisor for this proposed case report.

I trust that you will find this in order.

Kind regards.

……..
Prof JF Jooste
Head of Plastic and Reconstructive surgery
University of the Free State
Bloemfontein
051– 405 3544

Department of Plastic and Reconstructive surgery
Block , Room ,
Francois Retief Building
PO Box 339 (G35)
Nelson Mandela Drive
Faculty of Health Sciences
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Bloemfontein
9300

13 September 2018

The Chair: Health Sciences Research Ethics Committee
Dr SM Le Grange
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building
Po Box 339 (G40)
Nelson Mandela Drive
Faculty of Health Sciences
University of the Free State
Bloemfontein
9300

Dear Dr SM Le Grange

CASE REPORT TITLE: “Oromandibular Limb Hypogenesis Syndrome: A rare case illustrating shortcomings of current classification systems”

Enclosed please find the above proposed case report for your evaluation and approval.

Yours faithfully

Dr Lizanne Small
lizanne.small@gmail.com
072 841 7709

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Oromandibular-limb hypogenesis syndrome: A rare case illustrating shortcomings of current classification systems

by Lizanne Small

Mmed

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CASE REPORT

Oromandibular-limb Hypogenesis Syndrome: A Rare Case Illustrating Shortcomings of Current Classification Systems

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Bloemfontein

South Africa

Supervisor: Prof JF Jooste

Head of Department - Plastic and Reconstructive Surgery

Universitas Academic hospital

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Bloemfontein

South Africa

ABSTRACT

Background:

Oromandibular limb hypogenesis syndrome (OLHS) includes a spectrum of congenital anomalies that [redacted] anomalies. Their exact origin is unknown and most cases occur sporadically. Several syndromes are included under the umbrella of OLHS with considerable overlap in the phenotypical features between them. Two classification systems that of Hall (1971) and Chicarilli (1985) are currently recognised to classify OLHS.

Case Presentation:

A 3 month old male infant presented with clinical features that straddled more than one syndrome as classified under the OLHS. Given the oralfacial and extremity malformations of this case it could be classified as Hall Type IIIB or VB and Chicarilli Type IV. The aim of this case report was to contribute to understanding the difficulty in the classification of these complex malformations with our current classification systems.

Conclusion:

A modification of the Chicarilli classification that was proposed by Jung et al in 2016 made classification of this case possible. As a result from this case report it was clear that a review of current classification systems is needed with the aim to establish a new system where classification should be guided by predetermined major and minor criteria based on phenotypical features.

INTRODUCTION

Oromandibular-limb hypogenesis syndromes (OLHS) (OMIM 103300) represent a spectrum of congenital dysmorphic complexes that are characterized by abnormalities of the oral cavity and mandible (including: hypoglossia, aglossia, micrognathia, glossopalatine ankylosis, cleft palate, and gingival anomalies) as well as severe asymmetric limb defects (primarily involving distal segments).[1-3]

These malformations are extremely rare with an incidence of 1:175 000 live births and only a few cases have been reported in the literature to date.[1,3]

Several attempts have been made to explain the emergence of OLHS and the interaction of both genetic and environmental factors in the OLHS aetiology are acknowledged in the literature.[3] The majority of cases reported in the literature are sporadic but few have intra-familial history.[4]

Inheritance of mutated Msx2, a homeobox gene that is associated with craniofacial and limb malformation, has been proposed but till date, no genetic mutation or chromosomal abnormalities have been identified for this syndrome.[4-7]

Environmental factors likely to be the aetiology are maternal hyperthermia, maternal exposure to radiation and teratogenic drugs, intrauterine trauma/vascular accidents, chorionic villous sampling procedures, and maternal hyperthermia.[5,6,8-10]

Reports of exposure to drugs like Tigan, Benedictine, Imipramine, Diazepam, Chlorpromazine, and Meclizine suggest their involvement, but their effect in the causation of this syndrome has not been proved.[5,11]

There is considerable overlap between the syndromes gathered under the term OLHS, with a marked variability of face and limb anomalies as well as other additional malformations.[6] Some patients are difficult to classify because their stigmata bridge two or more syndromes.[12]

Hall in 1971 recognised five main categories. The only criteria necessary for inclusion is the occurrence of hypoglossia, with the exception of category Type V, which contains a miscellany of syndromes.[10,13] (Table: 1)

A new classification proposed by Chicarilli in 1985 in which the clinical presentation as well as the embryologic origin was taken into consideration.[10,14] He recognised four major classes: type 1 showing micrognathia, type 2 based on microglossia as the primary disorder from subtle microglossia to total absence of the tongue, type 3 presenting with glossopalatine ankylosis, including all intraoral bands that span the intermaxillary space, type 4 including Möbius and Charlie M syndrome. (Table: 1)

Table 1: Classification of syndromes of oromandibular and limb hypogenesis[15]

Hall (1971)	***Chicarilli (1985)***
Type I: A. Hypoglossia B. Aglossia	Type I: *Micrognatia* (mandibular) Pierre Robin syndrome Hanhart syndrome
Type II: A. Hypoglossia-hypodactilia B. Hypoglossia-hypomelia (peromelia) C. Hypoglossia-hypodactylomelia	Type II: *Microglossia* Hypoglossia Hypoglossia-hypodactyly
Type III: A. Glossopalatine ankyloses B. With hypoglossia C. With hypoglossia-hypodactilia D. With hypoglossia-hypomelia E. With hypoglossia-hypodactylomelia	Type III: *Dysgnathia* (maxilo-mandibular) Glossopalatine ankyloses Glossopalatine ankyloses hypodactyly
Type IV: A. Intraoral band and fusion B. With hypoglossia C. With hypoglossia-hypodactilia D. With hypoglossia-hypomelia E. With hypoglossia-hypodactylomelia	Type IV: Other Möbius syndrome Charlie M syndrome (Amniotic band syndrome)
Type V: A. Hanhart syndrome B. Charlie M syndrome C. Pierre Robin syndrome D. Möbius syndrome E. Amniotic band syndrome	

In order to correctly classify the different OLHS subtypes a proper phenotypical description of the orofacial and skeletal as well as other associated abnormalities of each syndrome is needed. Current classification systems lack a minimal criteria of absolute clinical features needed to diagnosis each of the OLHS subtypes. Some cases however present with stigmata that bridge two or more syndromes further complicating their diagnosis. Table 2 and 3 present the phenotypical features of OLHS illustrating the overlap between these syndromes.[16]

Table 2: Phenotypical description of OLHS to assist with diagnosis according to current literature:[16]

Hypoglossia-hypodactylia:	*Glossopalatine and ankylosis syndrome:*
Also called aglossia-adactylia syndrome, which is a misnomer since the tongue is never completely absent and the term "adactylia" does not convey the variation in limb defects of affected individuals.	Very rare syndrome with less than 30 cases reported in the literature so far and all reported cases appear to be sporadic.
1. Mouth: a. Mandible i. Micro/retrognathia ii. Oligodontia iii. Absent mandibular incisors with concomitant hypoplasia of the associated alveolar ridge iv. Other features a) Mild lower lip defect b) Microstomia c) Intraoral bands d) Oral frenula e) Oral syngnathia b. Tongue: i. Varying degree of hypoglossia ii. Ankyloglossia	i. Tongue itself or an intraoral band from the tongue a) Usually attached to the hard palate, or nasal septum if cleft palate b) May adhere to the maxillary alveolar ridge c) Mildly cleft tongue tip ii. High-arched or cleft palate iii. Hypoplastic mandible iv. Hypodontia principally affects the incisor teeth v. Ankylosis of the temporomandibular joint vi. Facial paralysis
2. Variable limb anomalies a. May involve any limb b. Distal reduction anomalies i. Oligodactyly (absence of some fingers and toes) ii. Adactylia (congenital absence of the fingers and toes)	Extremely variable limb anomalies a) Oligodactyly (absence of some fingers and toes) b) Syndactyly c) Polydactyly d) Peromelia (severe congenital malformation of the extremity,

iii.Peromelia (severe congenital malformation of the extremity, including absence of hand and foot) c. Syndactyly	including absence of hand and foot)
3. Other associated anomalies a. [redacted] b. Unilateral renal agenesis c. Imperforate anus	

Table 3: Phenotypical description of type V (Hall) / type IV (Chicarilli) OLHS syndromes[17]

	Orofacial	Skeletal	Other
Charlie M	facial asymmetry hypertelorism, telecanthus short philtrum micrognathia microstomia aglossia, hypoglossia absent teeth cleft palate gingival fibromatosis	ectromelia etrodactyly oligodactyly abnormal finger and toenail morphology	Macrotia (large ears) May exhibit caracteristics of Poland syndrome
Hanhart	facial asymmetry hypertelorism, telecanthus short philtrum micrognathia micostomia aglossia, hypoglossia absent teeth cleft lip/palate glossolabial adhesion	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia splenogonodal fusion cryptorchidism brain cysts intellectual disability
Möbius	as for Hanhart CN VII defect (major criteria) CN III, IV, VI, IX, X, XII defects possible external ear abnormalities	ectromelia, usually of all limbs etrodactyly oligodactyly clubbed feet	cases of gastroschisis and pulmonary hypoplasia seizures congenital cardiac lesions

Pierre-Robin	cleft palate glossoptosis micrognathia	Sometimes taped fingers, clinodactyly	20-40% isolated, otherwise part of other syndromes like Stickler

The aim of this case report was to contribute to understanding the difficulty in classification of these complex malformations with our current classification systems. Another objective was to do an in depth literature search for any other proposed classification systems that can address the shortcomings of the currently used classification systems proposed by Hall in 1971 and Chicarilli in 1985.

ETHICAL CONSIDERATIONS

Approval to present this case report was obtained from the Health Science Research Committee of the University of the Free State (serial number of ethical clearance:) as well as the Department of Health Research Data Base ( ). Consent to present this case report was obtained from the infant's mother and was also approved by the recognised ethics committees.

CASE PRESENTATION

Relevant history:

A two month old male infant was referred to the Plastic and Reconstructive outpatient department of Universitas hospital in March 2017 for workup of possible oromandibular-limb hypogenesis syndrome.

The infant was born at term via uncomplicated vaginal delivery to a 27 year-old gravida three with no prior miscarriages. The mother was on Atroiza, a combination anti-retroviral drug containing efavirenz/emtricitabine/tenofovir, throughout her pregnancy. She had unremarkable prenatal sonograms and denied any alcohol/drug abuse, or febrile episodes or illnesses during this pregnancy.

Main concern of mother was the tongue that was adhered to the hard palate with regurgitation of milk feed through the nose which complicated breast and bottle feeding.

Clinical examination:

The clinical evaluation revealed a normal head circumference and weight for age. The frontal hairline was in a normal position, inspection of the orbits revealed telecanthus (increased distance between the medial canthi of the eyes) and down slanting palpebral fissures. There was a flattened nasal bridge with normal midface height and volume. Bilateral low set ears with a deficiency of the superior thirds and lobbing of the helical rims was also present. (Figure 1)

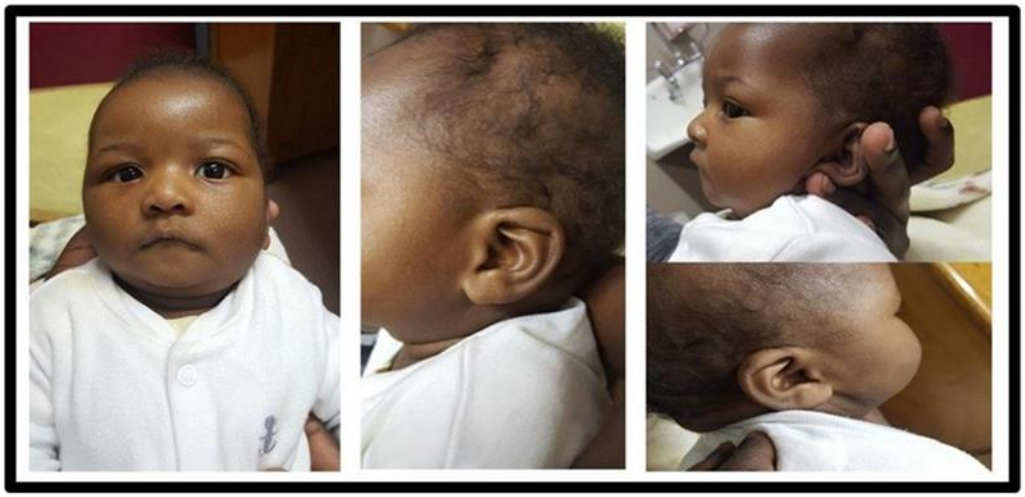

Figure 1: Illustrating the orofacial malformations

Oral examination showed a normal upper lip volume and a hypoplastic lower lip with down turned oral commissures. Micrognathia as well as retrognathia was evident with no airway obstruction clinically. Intraoral examination was difficult because of limited mouth opening due to the hypoplastic mandible. The tongue was adhered to the secondary palate with visible clefting of the secondary palate and a collapsed and hypoplastic alveolus on the right. (Figure 2)

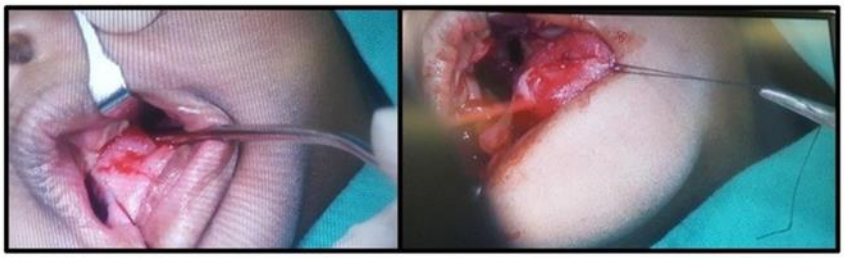

Figure 2: illustrating the intraoral findings of glossopalatine ankylosis

Examination of the trunk and back revealed no obvious pathology with normal male genitalia. The right upper limb showed hypomelia (deficiency of some or all parts of one of more limbs) with deficiency of the nails (anonychia) and fingertips of the second to fourth digits. The left upper limb showed hypomelia of the second to fifth digits with anonychia, patient also had hyponychia of the thumb nail. (Figure 3)

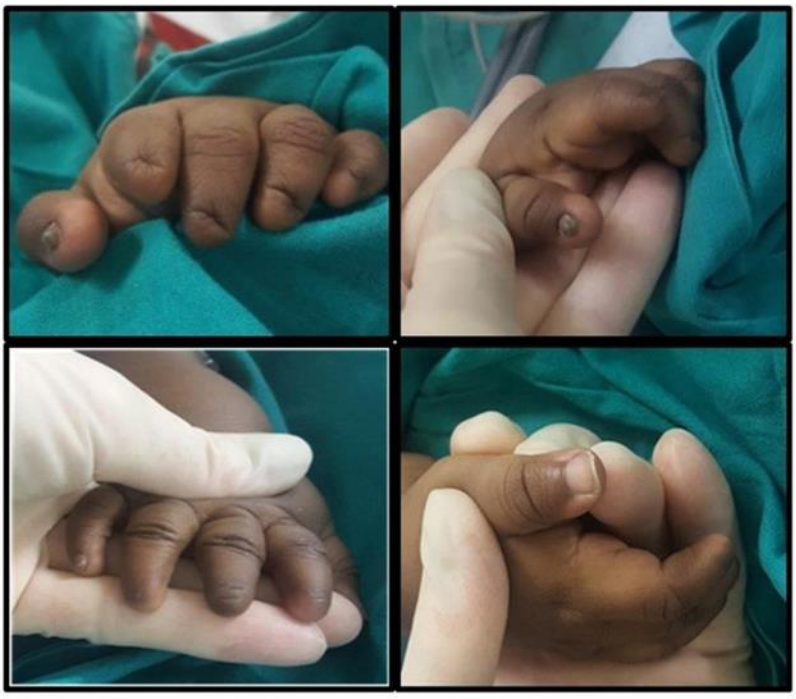

Figure 3: illustrating the upper extremity malformations

Examination of the lower limbs showed bilateral talipes equinovarus. The left foot had anonychia and hypomelia of the first and second toes, the right foot had anonychia and hypomelia of the first, second and third toes, with an incomplete syndactyly of the first webspace. (Figure 4)

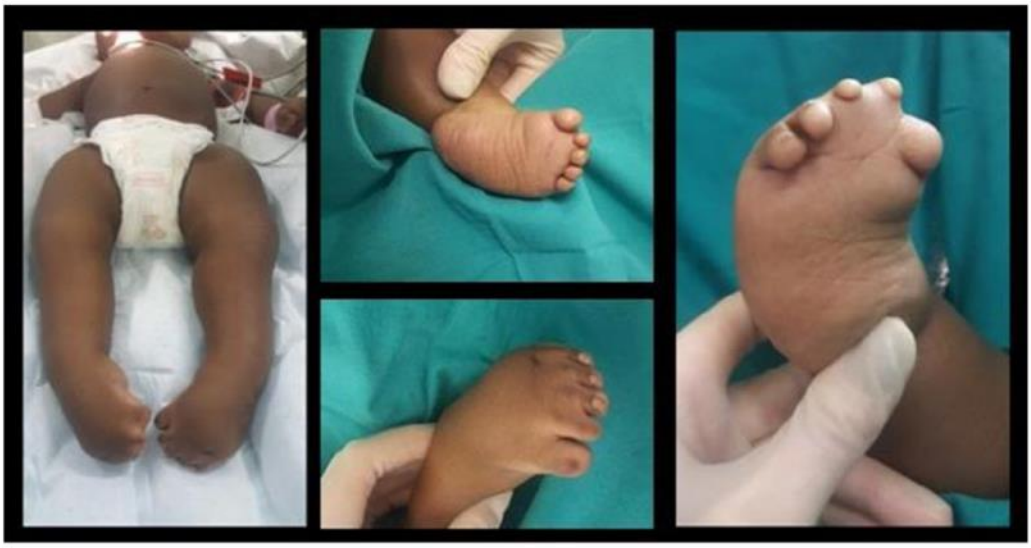

Figure 4: illustrating the lower extremity malformations

Diagnostic investigations:

Investigation that was performed included an echocardiography that showed no morphological or functional cardiac defects as well as an abdominal ultrasound excluded intra-abdominal pathology. Plain x-rays of the cervical spine and chest showed no skeletal abnormalities. X-rays of the hands and feet revealed hypomelia of the second to fifth distal phalanges of the left hand, and hypomelia of the second to fourth distal phalanges of the right hand. Left foot x-rays showed hypomelia of the first and second toe distal phalanges, and the right foot showed hypomelia of the first to third toes distal phalanges, with an incomplete syndactyly of the first web space. (Figure 5)

A contrasted computerized tomography of the facial bones and soft tissues showed the following: a midline defect in the hard palate creating a communication between the anterior nasal cavities and the oral cavity. The tongue could not be separated from

the anterior hard palate, with hypoplasia of the right alveolar ridge (Figure 6). Hypoplasia and retrusion of the mandible was also evident. Intracranial findings included: dilated lateral ventricles, a cavum velum interposition cyst, midline infratentorial dorsal cyst with slight mass effect on the cerebellar hemispheres. Intracranial findings most likely due to corpus callosum dysgenesis.

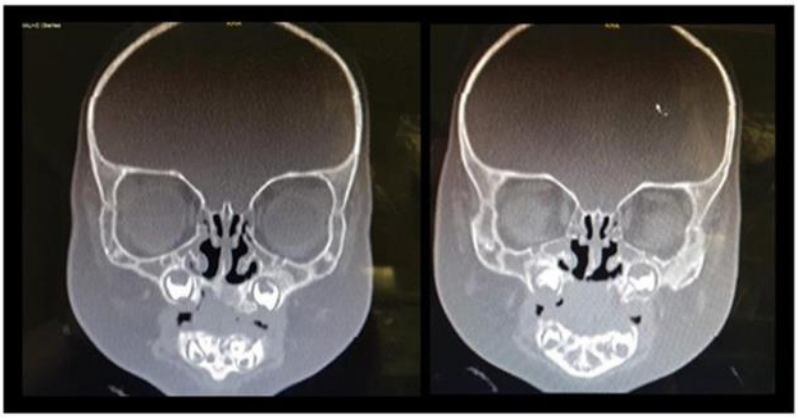

Figure 6: illustrating the CT findings

Management:

Management of the patient took place as part of a multi-disciplinary team. Genetic counselling was done by the genetics team explaining the possible aetiology and pathogenesis as well as the recurrence risk for future pregnancies. The paediatric orthopaedic department managed the clubbed feet with the Ponseti method (manipulative splinting in plaster of Paris casts).

Our Plastic and reconstructive team performed staged surgery for the glossopalatine ankyloses, by releasing the hypoplastic tongue from the hard palate in the first setting, (March 2018). This was followed by repair of the complete secondary palate cleft with a Von Langenbeck palatoplasty to address the hard palate defect and an intravelarveloplasty to repair the soft palate defect, performed in September 2018.

On future follow up speech will be closely monitored for velopharyngeal dysfuction. Orthodontic interventions may be needed in future as well as possible mandibular distraction osteogenesis or mandibular advancement. The fine motor function of the hand will need to monitored, the hypoplastic distal phalanges should theoretically not

interfere too much with function. The syndactyly of the right foot first web can be addressed in future for functional and cosmetic purposes.

DISCUSSION

As mentioned earlier OLHS in general and particularly the concordant syndromes are very difficult to diagnose due to their overlapping phenotypical features as well as the low incidence rate.[17]

As part of a general differential diagnoses for OLHS other syndromes and groups of syndromes like acrocephalosyndactyly/acrocephalo-polysyndactyly syndromes, orofaciodigital syndromes, and acrofacial dysostoses must be considered.[17]

The diagnosis of OLHS can usually be supported by a general patient history, clinical examination for orofacial and skeletal malformations, as well as genetic testing. In our case the mother was known with retroviral disease and on antiretroviral therapy, named Atroiza, in the pregnancy. Drugs like Tigan, Benedictine, Imipramine, Diazepam, Chlorpromazine, and Meclizine have been implicated in the aetiology of OLHS,[5,11] but there are no reported cases with exposure to antiretroviral therapy.

The mother reported no febrile disease during the pregnancy. There is evidence of maternal hyperthermia causing OHLS.[3,7,8] A range of defects including limb reduction, central nervous system (CNS) defects, facial dysmorphogenesis, and fetal death has been associated with maternal fever at/above 102°F between 4–14 weeks of gestation. Heat induced vascular disruption of the embryo has been implicated in the pathogenesis.[7,8] The extent, duration, and timing of the maternal fever predicts the nature of the anomalies and the most common consequence of gestational hyperthermia appears to be CNS defects. [6] However, patients with OHLS are often born with normal intelligence, so based on this, there is a need to explore maternal hyperthermia as a cause of the syndrome.

Several attempts have been made to explain the emergence of OLHS, Charlie M syndrome and glossopalatine ankyloses.[15,17] Defects in facial and limb differentiation usually occur during days 28–63 of the embryologic development. By day 32 the upper extremity development begins, it then further differentiates into the arm, forearm and

hand at day 37. The hand finally appears differentiated when the digits separate by day 46. Development of the lower extremity is delayed by about one week.[15,17]

The development of glossopalatine ankyloses can currently be explained by two possible theories.[18,19] One theory hypothesizes that persistence of the buccopharyngeal membrane (BPM) results in the appearance of intraoral bands. The BPM develops when the intraembryonic mesoderm does not invade all parts of the intraembryonic disc which results in separation of the stomatodeum entoderm and the foregut ectoderm up to day 26. As result of rapid growth of the pharynx, tongue and facial structures, the tension of the BPM becomes greater which leads to breakdown of this membrane.

The other theory hypothesize the persistence of a sub-glossopalatal membrane or ectopic membranes.[20] Between the sixth and eighth week of the embryonic development these membranes appear and normally disappear when the tongue descends around the ninth week. Membranous fusion between the upper and lower jaw can thus be the result of either the persistence of membranes, failure of the tongue to drop down or both.

In this case report an infant is presented with stigmata that straddle more than one syndrome as classified under the OLHS. The oral and limb deformities included: telecanthus, down turned palpebral fissures, a flat nasal bridge, and both ears were lobbed with constricted upper thirds. The patient also had microstomia with an underdeveloped lower lip as well as micrognathia. Intraoral examination showed glossopalatine ankyloses, a hypoplastic tongue was fused to the nasal septum with clefting of the secondary palate, with a hypoplastic and collapsed right alveolus. Skeletal malformations included hypomelia of the distal digits of the hands and feet, abnormalities of the finger and toenails as well as bilateral clubbed feet.
Based on these phenotypical findings the patient can be classified as a Hall IIID (glossopalatine ankyloses with hypoglossia-hypomelia) or Hall V (Charlie M syndrome), and a Chicarilli III or IV. (Table: 1)

Glossopalatine ankyloses has not yet been formally described as part of Charlie M syndrome according to current literature.[15] Grippaudo et al. came to the conclusion that glossopalatine ankyloses was an entirely new malformation after describing a case with phenotypical malformations of the face and extremities similar to Charlie M

syndrome. In 2016 Jung et al. reported a case with features suggestive of Charlie M syndrome and proposed a revised classification for OLHS.[17] They suggested renaming OLHS to "Oromandibular limb hypogenesis malformations" due to the synopsis of different syndromes, sequences and anomalies in one classification system. They also suggested changing Pierre Robin syndrome to Robin sequence and complete deletion of the amniotic band syndrome from the classification, because it only randomly results in malformations of the face and extremities. Table 4 illustrates the new classification of OLHS as proposed by Jung et al.

Table 4: New classification of former OLHS by Jung et.al: Oromandibular limb hypogenesis malformations (OLHM)[17]

	Type I:	**Type II:** *Dysgnathia with*	**Type III:** *Dysgnathia and glossopalatine ankyloses/intraoral bands of fusion with*	**Type IV:** *Miscellaneous*
A	Hypoglossia/ aglossia	Hypoglossia/ aglossia	Hypoglossia/ Aglossia	Hanhart syndrome
B	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Hypoglossia/ aglossia-hypodactyly	Möbius syndrome
C				Charlie M syndrome type I - no glossopalatine ankylosis
D				Charlie M syndrome type II – glossopalatine ankyloses
E				Robin sequence

By using this new proposed classification system the phenotypical findings of our case report will be in keeping with a Type IV D (Charlie M syndrome type II with glossopalatine ankyloses) (Table 4).

CONCLUSION

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There is considerable overlap between the syndromes grouped together under the umbrella of OLHS and there is controversy whether these syndromes are just varying presentations of the spectrum of OLHS.

Given the orofacial and limb malformations of this case it can be classified as a Hall IIID *or* VB and a Chicarilli type IV, illustrating the challenges in accurately classifying these syndromes. The new proposed classification by Jung et al. that renames OLHS to Oromandibular limb hypogenesis malformations is definitely an improvement and allows for the sub-classification of Charlie M syndrome (type II) that acknowledge glossopalatine ankyloses as part of the syndrome.

The exact aetiology of Charlie M syndrome is unknown. Some researchers believe that the syndrome may be caused by the interaction of several genes (polygenic inheritance) or that it may be inherited as an x-linked genetic trait or. In this case report the mother was on anti-retroviral drugs throughout the pregnancy and further research is needed to determine if there is an association between congenital orofacial and limb malformation with ARV therapy.

Beside the improved classification there is still a need for a more profound overview of the orofacial and limb abnormalities that occur in OLHS. A suggestion can be made that further sub-classification should rather be guided by a predetermined major and minor criteria system based on phenotypical features that still need to be established of OLHS.