

# Congenital Athelia and Cleft Palate: A Case Report of Two Generations

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## Abstract

Athelia is a rare condition and is almost always associated with other congenital anomalies. There is a heterogeneous pattern of associated clinical features and inheritance concerning this condition. In this case report, we reported a Chinese patient and her father with congenital athelia associated with cleft palate and sparse hair. Pedigree analysis suggests an autosomal dominant inheritance. A brief account on the related embryology, terminology and classification of the condition is reviewed. Possible underlying causes of the associated features and management issues are discussed.

## Key words

Absence of breast; Absence of nipple; Amastia; Amazia; Athelia

## Introduction

Athelia (absence of the nipple) is a rare condition. In 1965, Trier reviewed this condition and collected 43 cases from the literature since the first published report in 1839 in his historical review.<sup>1</sup> Most of the reported cases were associated with other congenital anomalies or presented as a manifestation of related syndromes e.g. Ectodermal dysplasia or Poland's syndrome. Moreover, different patterns of inheritance (autosomal recessive, autosomal dominant, X-linked recessive and X-linked dominant) were described<sup>1,2</sup> in the literature making the diagnosis and classification of this condition complicated and challenging.

In this case report, we would first describe a patient and her father born with this rare congenital anomaly together with cleft palate. An account on the related embryology and possible classification and causes will be followed. Pattern of inheritance will be discussed afterwards.

## Case Reports

### Case 1

Our female patient, HPS, was born in October 2006 by emergency lower segment Cesarean Section because of no progress during labour at 38 weeks and 5 days of gestation. Her birth weight was 3.22 kg and Apgar scores were 9 at 1 min and 10 at 5 min of life. Antenatally, patient's mother suffered from gestational diabetes mellitus controlled well by insulin. Antenatal USG scans did not reveal any fetal abnormalities at that time and her antenatal course was otherwise uneventful. Mother denied of taking any drugs or herbs other than insulin during pregnancy. Mother has given birth to a daughter with no congenital anomalies in 1997. Patient was admitted to the special care baby unit (SCBU) for the management of cleft palate and respiratory distress after delivery. She was later found to have Group B Streptococcus (GBS) sepsis which was managed uneventfully by intravenous antibiotics. Physical examination at birth showed bilateral absence of nipples, bilateral secondary cleft palate, tongue tie, right pre-auricular sinus, left low set ear and grade 2/6 ejection systolic murmur at left upper sternal border. There were no other dysmorphic features identified and examination on skin, respiratory system, abdomen and limbs were unremarkable. Echocardiogram was performed on day 12 and it showed patent foramen ovale and she was then discharged on

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day 14. Follow-up investigations were arranged.

Geneticists were consulted and commented that there was no conclusive syndromal diagnosis made. Chromosomal studies were normal (46, XX). USG brain at 3 months of age showed benign extra-axial collection in infancy, otherwise no congenital brain abnormality was detected. Repeated echocardiogram performed at 1 year of age showed closed patent foramen ovale and no other abnormalities.

Patient received repair surgery for cleft palate, release of tongue tie and excision of right pre-auricular sinus in August 2007 uneventfully. There is no delay or abnormal growth on teeth development. Sweat production has been normal. Clinical follow-up showed normal growth along centiles (Weight = 50th; Height = 75th; Head circumference = 75th). Development milestones have been appropriate for her chronological age. Physical examination at 2 years and 9 months of age revealed bilateral absence of nipple-areola complexes leaving with a faint mark on nipple area (Figure 1). She also has left-sided low-set ear (Figure 2) and sparse hair (Figure 3). Examination on cardiovascular, respiratory, abdominal, neurological, musculoskeletal systems, skin, nails and teeth are otherwise normal.

### Case 2

Patient's father, HKF, was born in 1954 by normal spontaneous delivery. He was noticed to have bilateral athelia and cleft palate since birth. He received repair surgery for cleft palate at 5 years of age. He noticed multiple reddish macular skin eruption and subcutaneous nodules

since the age of six. He did not consult any dermatologists before. The macules and nodules increase in number gradually throughout the years. He was diagnosed to have tuberculosis at the age of 18 and was treated completely. He had gastric ulcer with gastrointestinal bleeding at the age of 20 required partial gastrectomy. His sweat production has been normal. His teeth were not peg-shaped before though he is now having teeth prosthesis due to multiple dental caries. Physical examinations on cardiovascular, respiratory, abdominal, neurological and musculoskeletal systems are normal. There are bilateral athelia (Figure 4), multiple cherry-red macular lesions and subcutaneous



**Figure 2** Left low-set ear, taken at 2 years and 9 months of age.



**Figure 1** Bilateral absence of nipples, taken at 2 years and 9 months of age.



**Figure 3** Sparse hair, taken at 2 years and 9 months of age.

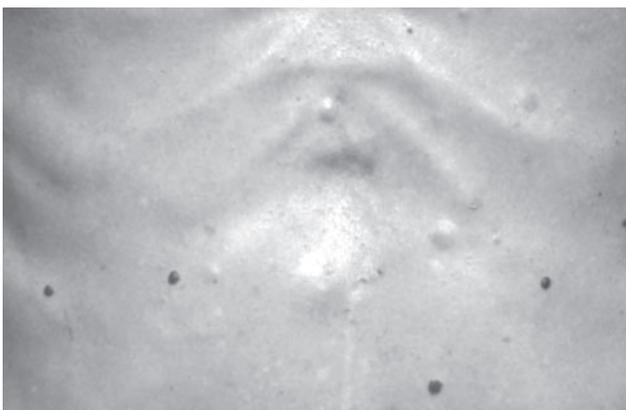
nodules (Figure 5) on chest wall and limbs. Skin biopsies on the lesions confirmed the diagnosis of Cherry haemangioma and Steatocytoma multiplex (multiple sebaceous cysts) respectively.

## Discussion

From the above illustration of 2 cases with congenital athelia and cleft palate involving the consecutive generation, underlying inheritable cause should be suspected. We would try to suggest an underlying cause of this rare condition in this family by reviewing the related embryology and current literature.



**Figure 4** Patient's father, bilateral athelia.



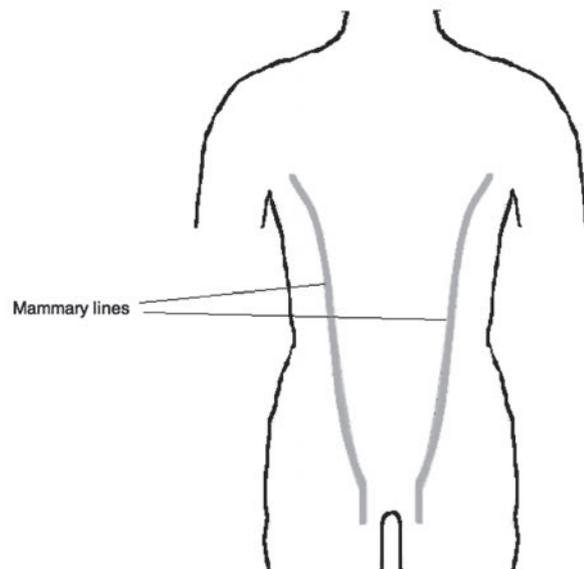
**Figure 5** Multiple Cherry haemangioma and Steatocytoma multiplex.

## Embryology

The mammary glands begin to develop during the sixth week of intrauterine life.<sup>3,4</sup> They first develop as bilateral ventral ectodermal solid growths into the underlying mesenchyme. These ingrowths grow along the mammary ridges or mammary lines bilaterally (Figure 6) extending from the axillary to the inguinal regions. As time passes, most of the ridge will disappear. Only those in the pectoral region persist due to an unequal proliferation of cells along the mammary line where the breasts are located. These result in the primary mammary bud. The primary mammary bud proliferates and gives rise to the secondary mammary bud which further develops into lactiferous ducts. The surrounding mesenchyme will develop into the fatty stroma and fibroelastic tissues of the mammary gland. These processes continue till late fetal stage when the epidermis overlying the site of origin of the mammary gland depressed, forming the shallow mammary pit. Soon after birth, the nipple will rise from the mammary pit due to the proliferation of the surrounding connective tissue of the areola and the nipple is then formed.

## Terminology

There are in fact multiple terms describing different defects related to this condition.<sup>1</sup> Athelia is defined as the developmental absence of the nipples. Amastia describes



**Figure 6** Mammary line.

the developmental absence of mammae (Synonymous with "breast").<sup>5</sup> Amazia describes the developmental absence of the mammary gland. Trier suggested the above terms are confusing and should use "absence of the breast" and "hypoplasia of the breast" instead.<sup>1</sup> "Absence of the breast" is defined by the absence of the nipples and breasts whereas nipples are typically present in "hypoplasia of the breast" but with decreased growth of the mammary gland.<sup>1,2</sup>

## Classification and Literature Review

Trier reported the largest series of this rare condition so far.<sup>1</sup> He classified the condition into 3 groups among the 43 cases: 1) Bilateral absence of the breast associated with congenital ectodermal defect; 2) Unilateral absence; and 3) Bilateral absence of the breast.

Trier documented 7 male cases belonging to the first group in his review.<sup>1</sup> The trait is sex-linked recessive. The associated defects mainly involve the skin, teeth, and nails. He described 20 cases grouping under the second group. Eighteen of them were associated with absence of corresponding pectoral muscles. These cases could be related to underlying Poland's syndrome which is identified by absence of the breast or hypoplastic breast unilaterally associated with absent pectoral muscles and other musculoskeletal defects ipsilaterally. He described 16 cases of bilateral absence of the breast grouping under the third group. Ten of them had no other anomalies associated. Only one of them was found to have bilateral absence of the breast and cleft palate. The others had various associated conditions e.g. high-arched palate, scant axillary and pubic hair, absence of a finger and lobster-claw deformity of hands and feet.<sup>1,2</sup> Familial inheritance was found in three of the pedigrees in Trier's review.<sup>1</sup> Two of them involved a two-generation transmission and the other involved a three-generation family.

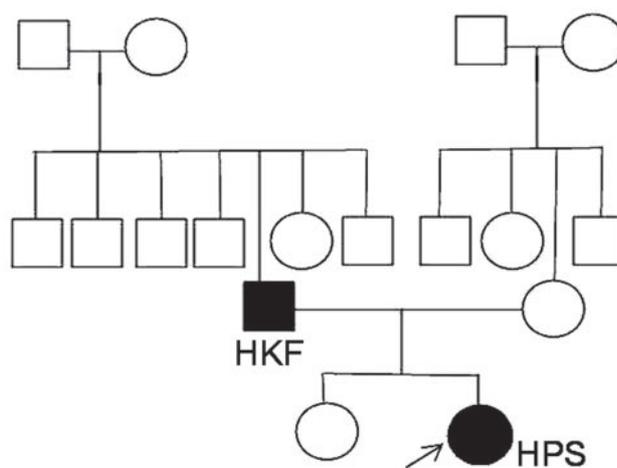
## Pattern of Inheritance

The family of our index patient consists of four persons. Patient's mother (born in 1972) and elder sister (born in 1997) are unaffected and enjoyed good past health. Both parents are of Chinese ethnicity and non-consanguineous. Further history of both sides of the family revealed no other affected individuals.

Published case reports in the literature reported different

modes of inheritance including autosomal recessive, autosomal dominant, X-linked recessive or X-linked dominant.<sup>1,2</sup> In our case, pedigree study suggests an autosomal dominant pattern of inheritance (Figure 7). The unaffected elder sister excludes a sex-linked dominant inheritance. Since there is no affected individual on paternal parents and all other 6 siblings, it may suggest a de novo mutation on patient's father as the underlying cause of this rare condition and has passed on to our patient.

We would classify our two patients under the third group of Trier's classification.<sup>1</sup> The association with cleft palate is rare and our cases add up to the 2nd and 3rd cases of the published reports so far. If we review the embryological development of the mammary glands and palate, the timing of the formation of mammary ridge and mammary bud coincides with the timing of the fusion of the fronto-nasal, lateral maxillary processes and the midline of the palatal shelf. Sommerlad<sup>6</sup> suggested that 1) Hypoplasia of the components, 2) Mechanical obstruction to fusion or 3) Breakdown of fusion could be one of the mechanisms responsible for fusion failure of the processes and giving rise to cleft palate. It is difficult to distinguish whether the underlying mechanism of congenital athelia is related to total under-development of the mammary ridge or the inability of differential cell proliferation involved in the formation of mammary bud in the pectoral area. The molecular biology of normal and abnormal growth of ectodermal cells during this period will be a good research topic to help us understand the embryogenesis of the condition.



**Figure 7** Pedigree, arrow=index patient, shaded=with athelia and cleft palate.

We are not sure if the multiple Cherry haemangiomas and Steatocytoma multiplex found on patient's father are associated features of this condition because they were not reported as such in the literature before and yet, they were not found on our index patient yet.

Despite our extensive search in the English literature, there were no published cases of Chinese ethnic origin with this rare condition so far. This could represent the rarity of this condition inherently or under-reporting of this condition in the English literature.

Management issues are expected to arise especially when our patient enters puberty and later during pregnancy. We anticipate that her breasts will not develop during puberty which could be a very embarrassing or distressing situation. It is of little doubt that construction of the breasts and nipples would be an option, but the timing and strategy of this operation will need further plan and discussion with plastic surgeons. Clinical psychologist's opinion will also be helpful with regards to the issues arising from the pubertal development in an adolescent girl.

## Summary

Athelia is a rare condition and is almost always associated with other congenital anomalies. Literature review shows a heterogeneous pattern of presentation in clinical features and inheritance concerning this rare condition. In this case report, we reported a Chinese

patient and her father with congenital athelia associated with cleft palate and sparse hair but without other ectodermal defects. Pedigree analysis suggests an autosomal dominant fashion of inheritance most likely arising from a *de novo* mutation on patient's father. To date, no definite gene locus is identified to explain this rare congenital anomaly. Further study in molecular genetics is required to locate the locus of the involving gene giving rise to it. Concerning the management of patients with this condition, apart from looking for and the management of the associated congenital anomalies, both physical and psychological issues should be expected to arise especially in a female patient. A multi-disciplinary approach involving Paediatricians, Plastic Surgeons and Clinical Psychologists would be the best option in the long term management of these patients.

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