

Case Report

Unmasking Pai syndrome: Emphasis on neuroimaging findings

Gokulsamy Arumugam¹, Vidushi Gupta¹, Megha Jain¹, M. Sarthak Swarup¹

¹Department of Radio-Diagnosis and Interventional Radiology, VMMC and Safdarjung Hospital, New Delhi, India.

***Corresponding author:**

M. Sarthak Swarup,
Associate Professor,
Department of Radio-Diagnosis
and Interventional Radiology,
VMMC and Safdarjung
Hospital, New Delhi, India.

sarthak163@gmail.com

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ABSTRACT

Pai syndrome is a rare syndromic variant of frontonasal dysplasia with combination of median cleft lip, cutaneous polyps, and midline lipomas of the central nervous system. This case report aims to describe the imaging findings in a patient with midline facial deformity and to evaluate the existing literature on Pai syndrome to understand its defining characteristics better. A 25-year-old female presented to the Plastic and Maxillofacial Surgery Outpatient Department with a congenital midline facial deformity. On examination, a midline cleft and a nasal polyp were observed. There were no signs of limb deformities and no history of seizures or intellectual disability. Computed tomography and Magnetic resonance imaging revealed corpus callosum lipoma with partial agenesis, elucidating the full spectrum of the syndrome. To detect potential associated anomalies, comprehensive brain imaging is advised for patients with midline facial clefts or skin masses. Additionally, genetic counselling and testing are essential to investigate underlying genetic causes. Long-term monitoring of both physical and neuropsychological development, supported by multidisciplinary care, is recommended to address the complex challenges posed by this condition effectively.

Keywords: Congenital facial malformation, Craniofacial dysmorphism, Developmental facial syndromes, Midfacial cleft, Midline facial anomalies, Neuroimaging, Pai syndrome

INTRODUCTION

Pai syndrome is a rare syndromic variant of frontonasal dysplasia, characterized by a distinctive combination of developmental anomalies, including median cleft lip or palate, facial hamartomatous polyps, and midline lipomas of the central nervous system.^[1] The syndrome exhibits considerable phenotypic variability, with only a few documented cases presenting with the full spectrum. The etiology of Pai syndrome remains unknown. Several recent studies have proposed potential diagnostic criteria for this rare condition; however, no consensus has been reached regarding the criteria to date. This case report highlights the imaging features of a patient with midline facial deformities and provides a comprehensive review of existing literature to advance the understanding of the clinical presentation, radiological findings, and diagnostic considerations of this rare entity.

CASE PRESENTATION

A 25-year-old female presented to the plastic and maxillofacial surgery outpatient department with a congenital midline facial deformity. On examination, a midline cleft involving the nose and upper lip was observed. A polypoidal mass fully covered by skin was also noted protruding

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through the left nostril. There were no signs of limb deformities, other anomalies, or any difficulties with vision or hearing. There was no history of seizures or intellectual disability.

A computed tomography (CT) scan of the head and face, including 3D reconstruction, was performed to evaluate potential bony and intracranial anomalies further and to assist in planning reconstructive surgery. The CT findings revealed a spectrum of abnormalities, leading to a diagnosis of this rare syndrome. Subsequently, magnetic resonance imaging (MRI) of the brain was conducted to look for any congenital brain anomalies. MRI revealed partial corpus callosum agenesis, with absent distal body and splenium, and a thickened, dysplastic genu, and proximal body. A well-defined, lobulated fat-density lesion (HU of -110) was seen on CT, anteriorly in the midline. The lesion demonstrated peripheral curvilinear calcification (bracket sign), with the anterior cerebral vessels seen coursing through its anterior portion. This fat-density lesion also extended into the right para-midline sulcal space of the right frontal lobe. In addition, the anterior midline falx appeared to be fenestrated, with interdigitation of the gyri. On MRI, it appeared homogeneously hyperintense on both T1-weighted

(T1W) and T2-weighted images, with signal suppression on fat-saturated sequences – consistent with the diagnosis of tubulonodular pericallosal lipoma [Figure 1].

Fronto-nasal dysplasia was noted, with a depressed nasal bridge. A smooth calvarial defect was observed in the anterior frontal bone, predominantly on the left side, with no obvious evidence of herniation of the meninges or brain parenchyma through it. Evidence of sub-galeal swelling was noted, with areas of fat attenuation overlying the defect. Widening of the bilateral ethmoidal sinus cavities, nasal cavity, and nares was noted. These findings were associated with hypertelorism in the form of increased interocular and binocular distances. In addition, a midline cleft lip and cleft palate were noted, with the incisive canal located in the midline maxillary alveolus [Figure 2].

A nasal dermoid was also noted, evident by a well-defined, hypodense, fat-density (HU of -95) polypoid lesion arising from the left nasal cavity with a focal calcific density completely covered by the skin. On MRI, the lesion was hyperintense on T1W images, and signal suppression was demonstrated on fat-saturated sequences [Figure 3]. Based on this constellation of imaging features, a diagnosis of Pai syndrome was established.

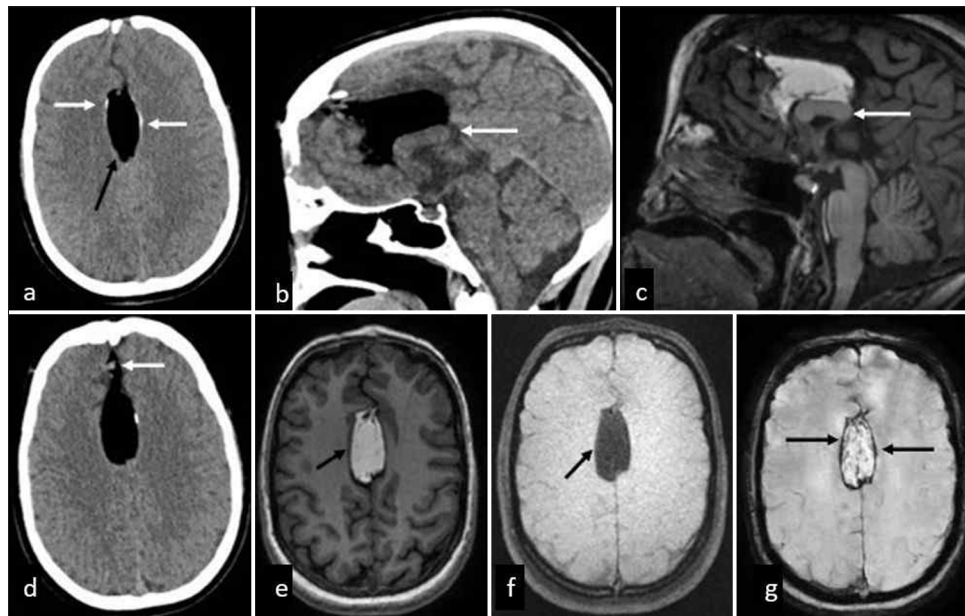


Figure 1: Lipoma of corpus callosum. (a) CT axial section of the brain shows well-defined fat density in the midline (black arrow) with evidence of bracket calcification (white arrows). (b,c) CT and MRI sagittal sections demonstrate partial agenesis of corpus callosum with absent distal body and splenium (white arrow). (d) CT axial section reveals extension of fat-density into the right para-midline sulcal space of the right frontal lobe (white arrow). (e,f) MRI axial sections reveal midline homogeneously hyperintense lesion on T1W image showing fat suppression, suggestive of tubulonodular corpus callosum lipoma. (g) Blooming artifacts on susceptibility weighted image noted along the periphery of the lesion (black arrows) mimicking hemorrhage, characteristic of an intracranial fat-containing lesion.

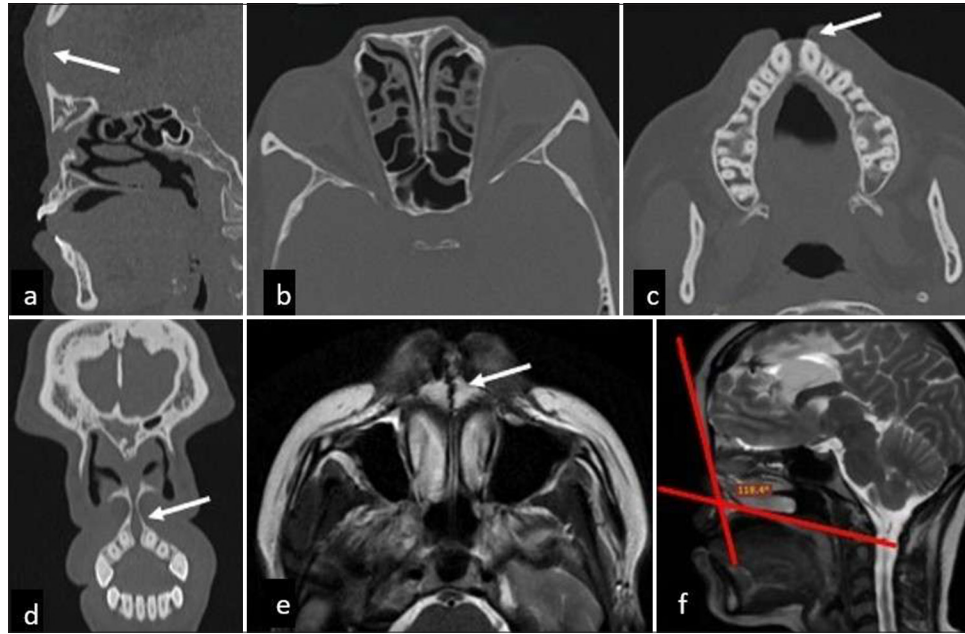


Figure 2: Frontonasal dysplasia. (a) CT sagittal section shows calvarial defect in the anterior frontal bone (white arrow) with no evidence of cephalocele. (b) CT axial image shows widening of bilateral ethmoidal sinuses and nasal cavities with associated hypertelorism. (c,d,e) Axial and coronal CT sections and MR axial section show midline cleft involving upper lip and palate (white arrows). (f) MR sagittal section demonstrates frontonasal dysplasia with flattening of the midface and a widened fronto-maxillary angle measuring $\sim 118^\circ$.

DISCUSSION

Pai *et al.*^[1] identified the primary features of Pai syndrome as a median cleft of the upper lip, nasal skin masses, and lipoma of the corpus callosum. Additional associated anomalies include clinodactyly, umbilical hernia, and cryptorchidism. Morice *et al.*,^[2] in their case study, proposed that congenital nasal or mediofrontal skin mass or a mid-anterior alveolar process polyp regardless of the pathological diagnosis such as dermoid, hamartoma, or lipoma should be considered as an obligatory criterion in the diagnosis of Pai syndrome with atleast one of the following criteria: Midline cleft of upper lip or palate and/or pericallosal lipoma or interhemispheric lipoma in the case of corpus callosum dysgenesis. In a study by Mishima *et al.*,^[3] 11 out of 14 patients exhibited nasal polypoid skin masses. Among these, the polypoidal mass was attached to the nasal septum in seven patients and to the alveolar cleft in four patients. Histological examination revealed mature adipose tissue with normal skin in six out of nine patients assessed.

Midline facial clefts are extremely rare within the cleft lip and palate population, with an occurrence rate ranging from 0.43% to 0.73%.^[4] Two primary hypotheses have been proposed to explain the development of midline facial clefts: Classical fusion theory and Veu's mesodermal penetration theory. According to classical fusion theory, normal facial formation involves the growth and union of bilateral

maxillary processes with the unpaired frontal process in the midline. Veu's theory, on the other hand, stated that mesodermal tissue initially present during development penetrates the epithelial wall of the primary palate laterally, forming the upper lip and premaxilla. A disruption in this mesodermal penetration results in a median cleft lip.

Wiemer *et al.*^[5] categorized midline facial malformations into two groups based on their association with hypertelorism or hypotelorism. Cases associated with hypertelorism were linked to frontonasal dysplasia, while those with hypotelorism were associated with holoprosencephaly. Sedano *et al.*^[6] elaborated that frontonasal dysplasia and holoprosencephaly represent opposite ends of the spectrum of midline facial malformations.

Pericallosal lipomas are the most prevalent type of intracranial lipomas and are commonly associated with agenesis or dysgenesis of the corpus callosum. Development of intracranial lipomas is attributed to the over-proliferation of fat cells within the leptomeninges. Two types of intracranial lipomas have been identified: Tubulonodular and curvilinear. The tubulonodular type is the most frequent, located anteriorly, and often associated with extensive callosal and frontonasal anomalies. In contrast, the curvilinear type is thinner and typically located posteriorly.^[7] Pascual-Castroviejo *et al.*^[8] reported that all eight of their patients with frontonasal dysplasia had corpus callosal lipomas, and



Figure 3: Nasal dermoid. (a) CT sagittal section demonstrates a well-defined fat-density polypoid lesion arising from the left nasal cavity (white arrow) with a small calcific focus (not shown) consistent with nasal dermoid. (b,c) MR axial sections show a hyperintense polypoid lesion on T1W image with signal suppression on fat-saturated image (white arrow).

none experienced seizures or headaches. However, epilepsy is consistently observed in patients with corpus callosal lipomas unrelated to Pai syndrome or frontonasal dysplasia. Notably, our patient also had no history of seizures. Savasta *et al.*^[9] reported the case of a female showing normal karyotype with facial features characteristic of Pai syndrome as described by Coban *et al.*,^[10] such as bifid nose and alopecia. The patient also presented with midline lipoma and partial agenesis of the corpus callosum.

In a case report by Ochoa *et al.*,^[11] two small ventricular septal defects, one muscular and the other perimembranous, were detected sonographically in a fetus with Pai syndrome. In addition to other facial features, Nibhanupudi *et al.*^[12] demonstrated vomer bone agenesis with nasal floor lipoma in a patient with Pai syndrome. Pai *et al.*^[1] reported that hereditary inheritance does not play a significant role in Pai syndrome. However, Masuno *et al.*^[13] identified a *de novo* reciprocal translocation, $\times 46, t(X;16)(q28;q1.2)$, in their patient. Notably, this patient did not present with corpus callosal lipoma, which created a diagnostic challenge. Similarly, Mishima *et al.*^[3] speculated that a chromosomal abnormality could be involved, although they could not confirm this cytogenetically.

Surgical management includes cheiloplasty and removal of midline polyp in a single session, usually done at 3–6 months of age, followed by correction of nasal pyramids, usually done after puberty to allow the growth of nasal bones. Management of skull base encephaloceles includes intradural resection of herniated brain tissue with duraplasty. Intracranial lipomas are considered “leave me alone” lesions as they are rarely symptomatic and surgical removal carries a high risk as they tend to encase the cerebral vessels and nerves.^[14]

In our patient, the sole presenting complaint was a midline facial deformity, with no history of seizures or intellectual disability. There was no notable family history. Imaging findings revealed a tubulonodular type of pericallosal lipoma with partial corpus callosum agenesis, frontonasal dysplasia with associated hypertelorism, median cleft lip and

palate, and a nasal dermoid. Although a genetic study was recommended, it was declined due to the patient’s financial constraints. The patient has now been scheduled for facial reconstructive surgery.

Differential Diagnosis

The differential diagnosis of Pai syndrome includes frontonasal dysplasia, Aicardi syndrome, basal frontonasal encephalocele, holoprosencephaly, and Goldenhar syndrome. Frontonasal dysplasia can show midline facial defects but does not have brain lipomas. Aicardi syndrome may show absence of the corpus callosum but is usually associated with seizures and eye abnormalities and does not show nasal polyps. Basal encephalocele presents as a midline nasal mass with a skull base defect and herniation of brain tissue. Holoprosencephaly shows abnormal separation of the forebrain. Goldenhar syndrome mainly affects the side of the face and ears. The presence of nasal polyps along with corpus callosal agenesis and pericallosal lipoma supports the diagnosis of Pai syndrome.

CONCLUSION

Pai syndrome is an uncommon disorder characterized by significant phenotypic variability. Proper evaluation is crucial for patients with a midline facial cleft or a skin mass to ensure accurate diagnosis. Comprehensive brain imaging is recommended to identify potential associated abnormalities, alongside genetic counselling and testing to explore underlying genetic factors. Long-term monitoring of both physical and neuropsychological development is vital for these patients. Management typically involves a multidisciplinary team, including specialists such as maxillofacial surgeons, neurosurgeons, plastic surgeons, head and neck surgeons, radiologists, pediatricians, pediatric neurologists, and geneticists, to effectively address the complex needs of the condition.

Author contributors: M.J. and M.S.S. were involved in the conceptualization, complete design of the case study, and the

interpretation of findings. G.A. and V.G. were involved with the acquisition and interpretation of images, writing the manuscript, and literature review. M.J., M.S.S. contributed to editing the article, critical review, and drafting the final version submitted. All authors read and approved the final manuscript.

TEACHING POINTS

1. Pai syndrome should be considered in any patient presenting with midline facial clefts or cutaneous nasal polyps, as early recognition allows timely evaluation for associated intracranial anomalies.
2. Comprehensive neuroimaging, particularly magnetic resonance imaging is essential for identifying pericallosal lipomas and corpus callosum dysgenesis, which are key diagnostic components and guide appropriate multidisciplinary management.

MCQs

1. Which of the following triads best represents the classical features originally described by Pai *et al.* in Pai syndrome?
 - a. Hypertelorism, nasal dermoid, and holoprosencephaly
 - b. Median cleft of upper lip, nasal/medial frontal skin polyps, and corpus callosal lipoma
 - c. Bifid nose, calvarial defect, and encephalocele
 - d. Cleft palate, clinodactyly, and ventricular septal defect

Answer key: b

2. Which intracranial lipoma subtype is most commonly associated with extensive callosal and frontonasal anomalies in Pai syndrome?
 - a. Curvilinear lipoma
 - b. Peripheral cisternal lipoma
 - c. Tubulonodular lipoma
 - d. Quadrigeminal plate lipoma

Answer key: c

3. According to proposed diagnostic criteria, the presence of which of the following is considered obligatory when diagnosing Pai syndrome?
 - a. Hypertelorism
 - b. Cleft palate
 - c. Congenital nasal or medial frontal skin mass
 - d. Agenesis of the corpus callosum

Answer key: c

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