CASE REPORT

# Solitary Median Maxillary Central Incisor in Hartsfield Syndrome: A Case Report

Patricia MP Reis[1], Jorge Faber[2], Jéssica SO Rosa[3], Mike Bueno[4], Maurício Barriviera[5], Érica N Lia[6]

## Abstract

Hartsfield syndrome is a rare and unique clinical combination of ectrodactyly and holoprosencephaly (HPE) with or without cleft lip and palate, as well as various additional characteristics. Although several genes responsible for HPE and ectrodactyly have been identified, the genetic origin of Hartsfield syndrome remains unknown, as there are few reports in the literature. The objective of this case report is to present dentofacial abnormalities in an 11-year-old boy with Hartsfield syndrome, who presented mental retardation, hearing loss, bilateral hand and foot ectrodactyly, HPE, and solitary median maxillary central incisor (SMMCI) besides 12 dental ageneses.

**Keywords:** Anodontia, Craniofacial anomalies, Hartsfield syndrome.

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## Introduction

The Hartsfield syndrome results from heterozygous or biallelic variants in fibroblast growth factor receptor 1 (FGFR1).[1] It is characterized by the co-occurrence of ectrodactyly and HPE.[2,3] Very often it includes midline defects, such as microcephaly, midface hypoplasia, cleft lip and/or palate, and a single central incisor.[3] The first case was reported by Hartsfield et al. in 1984[4] and there have been just a few reports since then, affecting only males.

The clinical presentation of Hartsfield syndrome often includes developmental defects, such as isolated hypogonadotropic hypogonadism, secondary hypernatremia, mild to severe intellectual disability, central diabetes insipidus, hypo or hypertelorism, and malformed ears. There are also reports of skull defects, radial aplasia, vertebral anomalies, cardiac malformation, and ocular anomalies.[1]

Although several causative genes for HPE and ectrodactyly have been identified, the genetic cause of Hartsfield syndrome is still being investigated.[1–3,5] Dominant or recessive mutations of the FGFR1 are present in Hartsfield syndrome,[1,2,6,7] consistent with the known roles of this receptor in vertebrate ontogeny. It is postulated that mutations in a single key developmental gene support the co-occurrence of HPE and ectrodactyly, despite the variable expression of the syndrome.[8,9] The gene responsible for the syndrome remains unknown; however, it is speculated that a multifactorial origin with an important gene linked to the X chromosome is involved.[3,9] This could explain the absence of the syndrome's occurrence in women, as well as its intrafamilial recurrence.[3,9]

The description of oral and dental changes associated with this syndrome is scarce and poorly detailed in the scientific literature.[2,3,6,8,9] The objective of this case report is to present the oral-dental aspects of an 11-year-old boy with a diagnosis of Hartsfield syndrome emphasizing the SMMCI.

## Case Description

An 11-year-old boy patient with the diagnosis of Hartsfield syndrome was referred to the Dental Clinic of the University Hospital of Brasília due to "poor tooth formation and absence of one of the upper central incisors."

The clinical history revealed that the mother had a previous miscarriage at 2nd month of gestation. The child's intrauterus development was normal until the 7th month, when cerebral malformations were observed *via* ultrasound examination, but without a definitive diagnosis at this time. The child was born by cesarean delivery at 38 weeks of gestation and remained in the pediatric intensive care unit for 4 days due to respiratory problems at birth. After hospital discharge, the child was referred to the International Center for Neuroscience and Rehabilitation (SARAH Network of Rehabilitation Hospitals, Brasília, Brazil), where genetic mapping was performed. At 2-year-old, the patient was diagnosed with Hartsfield syndrome. At 5-year-old, he underwent cryptorchidism correction surgery.

As general characteristics, the patient presents HPE, hearing loss (hearing aid use), hypernatremia, psychomotor developmental delay, moderate mental retardation, irritability, and difficulty related to urinary sphincter control. Currently, he is actively taking antipsychotic medication (periciazine) besides psychotropic medication (methylphenidate hydrochloride). His parents reported

[1–3,6]School of Health Sciences, University of Brasília, Brasília, Brazil

[4]Department of Imaging and Radiology, Faculdade São Leopoldo Mandic (SLMANDIC), Brasília, Distrito Federal, Brazil

[5]Brasília, Brazil

**Corresponding Author:** Patricia MP Reis, School of Health Sciences, University of Brasília, Brasília, Brazil, Phone: +5561983484228, e-mail: patriciapizzoreis@gmail.com

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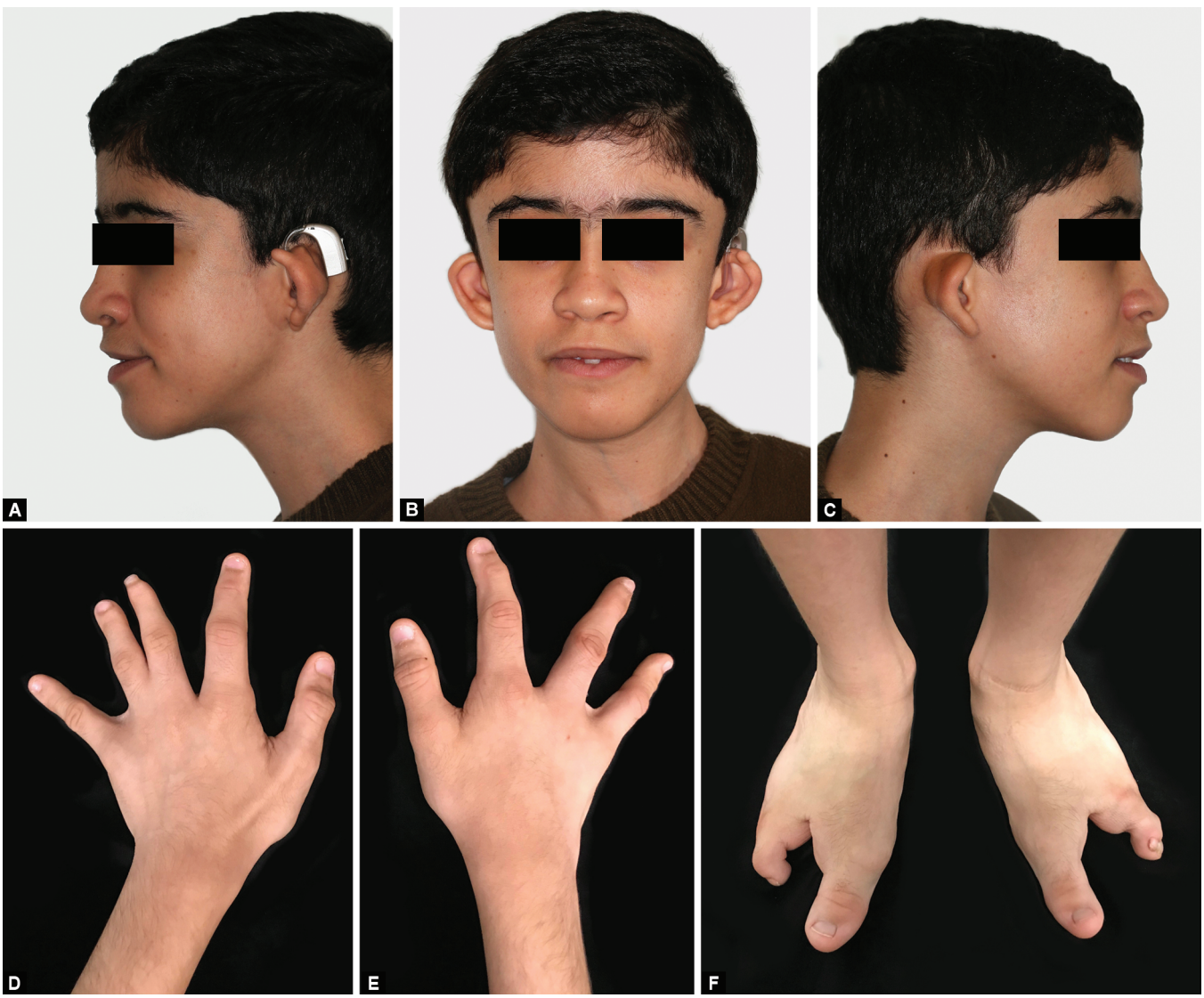
that he attends school and has noticed a progressive improvement in relation to psychomotor development and language, and his diet is healthy.

At the extraoral examination, it was observed that the frontal facial analysis (Fig. 1B) showed a correct proportion of the upper, middle, and lower facial thirds; slightly deficient zygomatic projection; right and left ear shells lateralization; prominent ears; the presence of an extra tubercle at the top of the left ear; left converging right eye strabismus; bilateral epicantal folds; and broad nasal bridge. Lateral analysis (Figs 1A and C) showed a straight profile, both suitable chin-neckline, and angle of chin-neckline. The nasolabial angle is closed.

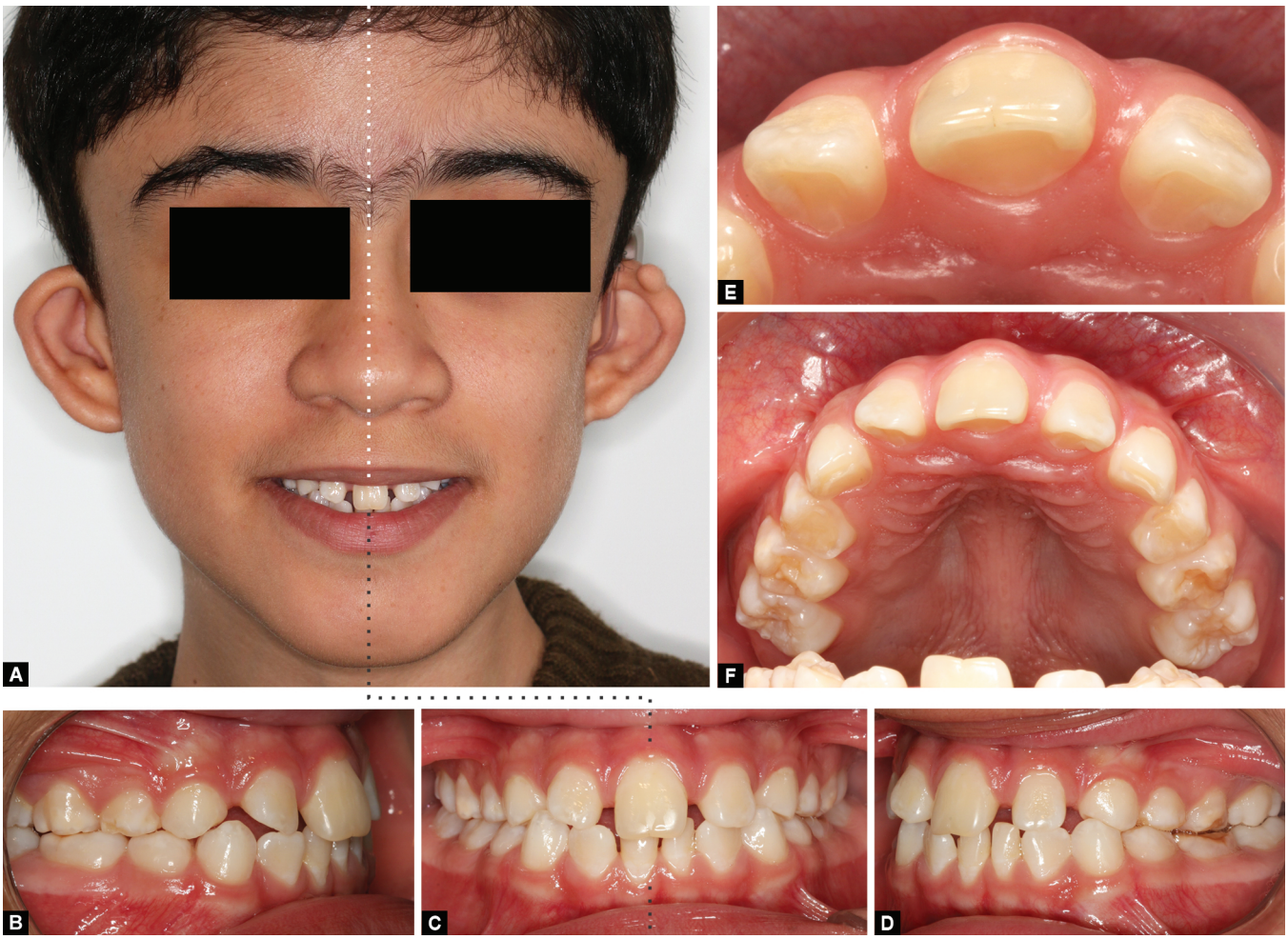
The patient presents bilateral ectrodactyly in the hands and feet. In the right hand (Fig. 1E), there is a total absence of finger three. The left hand (Fig. 1D) presents all the fingers but shows the malformation of the distal phalanges of fingers three and four. Figure 1F shows the complete absence of fingers two, three, and four of both feet.

Intraoral analysis revealed that the patient was in the intertransient period of mixed dentition, with good control of dental biofilm and absence of carious lesions. Figure 2C showed that the permanent inferior central incisors have a conoid shape. Intraoral lateral photos showed a class I molar relationship (Figs 2B and D). An SMMCI was identified, as well as a diastema between it and the lateral incisors (Figs 2C to F). In the frontal photo of the smile (Fig. 2A), we can see the relationship between the single central incisor and the facial midline.

According to cone beam computed tomography (CBCT), 13 dental ageneses were identified (Figs 3C and D)—upper central incisor (eight or nine), upper first premolars (5 and 12), upper and lower second premolars (4, 13, 20, and 29), lower second molars (31 and 18), and upper and lower third molars (1, 16, 17, and 32), characterizing oligodontia. Figures 3A and B show tomography images with the position of the permanent lower canines in buccally displaced.




**Figs 1A to F:** (A to C) Facial and profile photos, left, and right; (D) Hypertelorism, convergent strabismus, broad nasal bridge, low implantation of malformed ears, extra tubercle at the top of the left ear, and straight profile; (E) Bilateral ectrodactyly in the hands; (F) Complete absence of fingers two, three, and four of both feet




**Figs 2A to F:** (A) Smiling facial photo with the presence of a single incisor; (B to D) Right and left lateral intraoral photos—relationship of deciduous canines and permanent molars in class I. Frontal intraoral aspect; (E and F) The presence of a single upper permanent central incisor is noted. Upper arch—single permanent central incisor

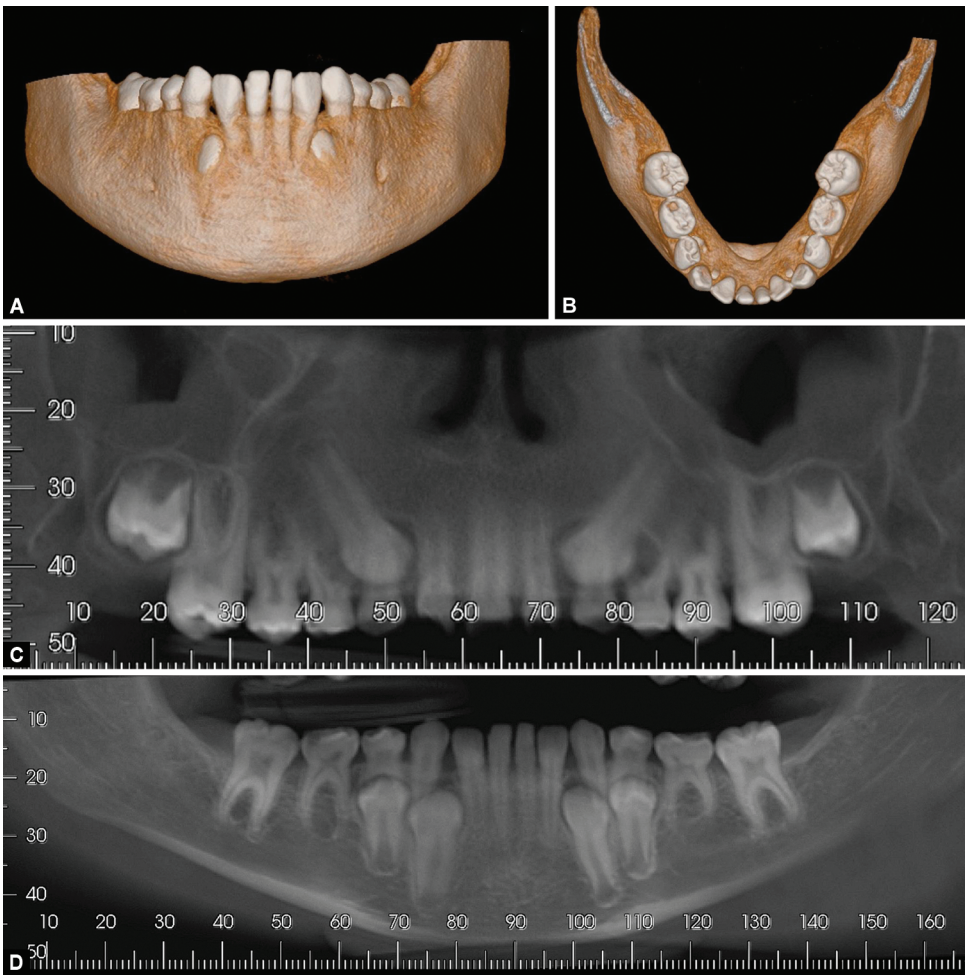
One fact that caught our attention was the position and shape of the SMMCI. Figures 4B, D, , and and E show the position of this tooth practically in the midpalatal raphe, equidistant from the right and left upper lateral incisors. Regarding its shape (Figs 4A and C), we find it difficult to determine whether this incisor is tooth eight or nine, with very similar mesiobuccal and distovestibular angles and a malformation in the middle of the incisal (invagination of the incisal enamel). Figure 4D shows tomography images with the position of the upper canines in lingual displace.

## Discussion

Hartsfield syndrome is a rare condition that involves simultaneous HPE (1:10,000 births)[7] and ectrodactyly (1:18,000 births). The occurrence of cleft lip and palate in Hartsfield syndrome is variable[2] and was not present in the case described. Until January 2021, just 15 case reports or case series were identified at PubMed.

An SMMCI syndrome is a rare malformation (1:50,000 live births) associated with defects of midline structures, including the nasal airways, craniofacial bones, and the brain (HPE), along with an increased risk of pituitary malfunction and malformation.[10] This single incisor is symmetrical and can be present in the deciduous as well as in the permanent dentition.[11] The syndrome can occur as a mild form of the broad HPE spectrum, but can also be associated with other characteristics. The etiology is still largely unknown,[10–12] but the syndrome is probably based especially on genetic causes. Early recognition of the syndrome is of great importance for establishing the diagnosis, for additional investigation, for possible treatment of associated anomalies, and for the correct advice concerning the risk of inheritance of severe congenital birth defects related to HPE. The presence of a single central incisor, in this case, is associated with HPE present in Hartsfield syndrome. The association of HPE with SMMCI in Hartsfield syndrome is being described for the first time in the literature, becoming a very important clinical finding. It is extremely important to call attention to the interesting and atypical shape of the single central incisor since there is no clear laterality in its dental anatomy.

Descriptions of dental malformations or agenesis associated with Hartsfield syndrome are rare. Although the absence of a central incisor has previously been reported in the literature,[2,3] there is no mention of oligodontia. Oligodontia is defined as the absence of six or more teeth, excluding third molars.[13] In this case, agenesis of nine teeth were identified,




**Figs 3A to D:** CBCT with the absence of tooth germs 1, 4, 5, 8 or 9, 12, 13, 16, 17, 18, 20, 29, 31, and 32: (A) Mandibular front view; (B) Mandibular axial view; (C) Upper panoramic view; (D) Lower panoramic view

excluding third molars. Dental agenesis is the most common craniofacial malformation in humans and may occur as an isolated nonsyndromic trait or be associated with several other syndromes or oral slips.[14] Recent research suggests that both environmental factors and genetic regulation are involved in the etiology of this condition, with the former playing a more important role. The agenesis is a hereditary anomaly and suggests that transmission is determined by an autosomal dominant gene with incomplete penetrance and variable expressiveness.[15] For this reason, recent efforts have focused on identifying specific genes that are involved in the regulation of dental development. About >300 genes are expressed and involved in teeth morphogenesis, including Msh Homeobox 1 (MSX1), Paired Box 9 (PAX9), AXIS inhibition protein 2 (AXIN2), anhidrotic ectodermal dysplasia (EDA), sprouty homolog 2, transforming growth factor α, sprouty RTK signaling antagonist 4, Wnt family member 10A, FGF3, FGF10, FGFR2, and bone morphogenetic protein 4.[16,17] Among these genes, PAX9, MSX1, AXIN2, and EDA are most frequently associated with nonsyndromic dental agenesis.[18,19] In this clinical case, we cannot make the association of Hartsfield syndrome with oligodontia since the genetic mapping of this dental abnormality has not been done. But, as we said, we can associate this syndrome with SMMCI.

## Conclusion

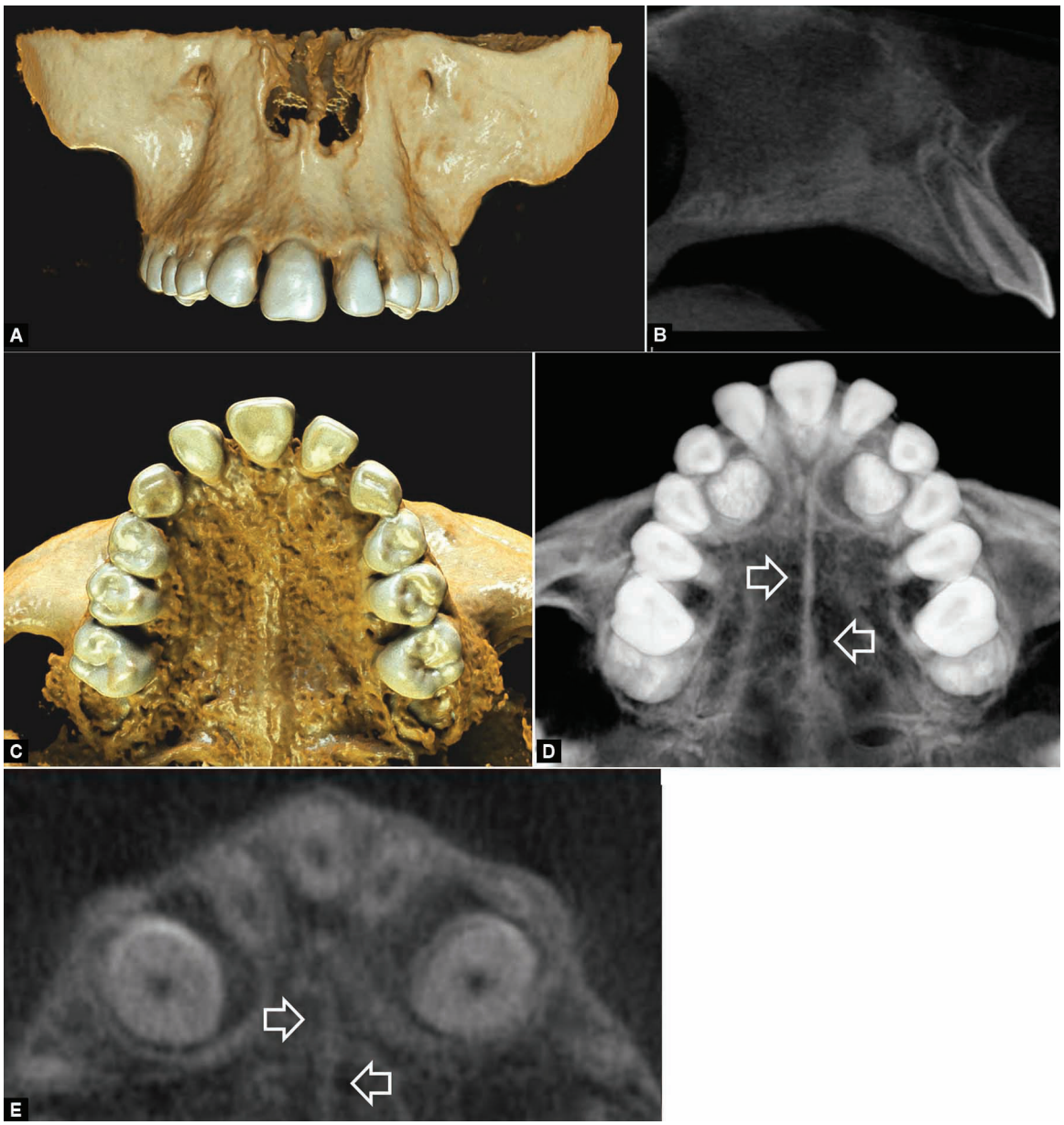
Due to the rarity of the syndrome, there are few cases documented in the literature (only 15), and descriptions of dental findings can complement the syndrome's description, aiding in future diagnoses. So far, in none of the published papers has an analogy been made between HPE with SMMCI and Hartsfield syndrome. In the described case of an 11-year-old boy with Hartsfield syndrome, 13 dental ageneses were identified.

## Disclosure

This article is a part of the author's (Dr. Patrícia Maria Pizzo Reis) dissertation titled "Biologia, Morfologia, Fisiologia, Estética, Arte e Ortodontia" archived in the "Universidade de Brasília Repository" (https://repositorio.unb.br/handle/10482/43818).

## Data Availability

The data underlying this article are available in the manuscript.




**Figs 4A to E:** SMMCI in relation to the midpalatal raphe: (A to E) The images show the position of the upper canines in lingual displace

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