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# Solitary median maxillary central incisor syndrome: cone beam computed tomography illustrated review

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## Abstract

The solitary median maxillary central incisor syndrome (SMMCI) is a rare autosomal dominant genetic syndrome characterized by the presence of a single central incisor positioned along the midline in both primary and permanent dentition. It is often associated with the holoprosencephaly spectrum, a group of brain and facial malformations. The etiopathogenesis of SMMCI is believed to involve embryonic developmental defects occurring between the 35th and 38th day of gestation, primarily affecting midline facial structures. Several genetic factors, including mutations in the Sonic Hedgehog gene on chromosome 7 and other genetic variants, have been implicated in SMMCI development. Diagnosis is typically made through clinical examination, prenatal ultrasound, and postnatal dental evaluation. Management of SMMCI requires a multidisciplinary approach involving pediatricians, otolaryngologists, neuro-pediatricians, and genetic counselors. Dental interventions may include extraction and space maintenance, orthodontic treatment, prosthodontic options, or esthetic considerations. Further research is needed to understand better the underlying mechanisms and genetic factors associated with SMCI, which will contribute to improved diagnosis and management of this syndrome.


**Keywords**: Solitary median maxillary central incisor syndrome, orphan disease, holoprosencephaly, CBCT, cyclopia.

## Introduction

Solitary median maxillary central incisor syndrome (SMMCI) was first described by Scott in 1958 [1]. This rare autosomal dominant genetic disorder is characterized by the development of a single central incisor positioned symmetrically on the midline in both the primary and permanent dentitions [2]. Epidemiological studies have estimated the prevalence of SMMCI to be approximately 1 in 50,000 births, with some evidence suggesting a potential female predisposition [3].

Beyond its dental characteristics, SMMCI is sometimes associated with more complex syndromic conditions, notably holoprosencephaly (HPE), where the brain does not properly divide into distinct hemispheres [4]. This association places SMMCI within the spectrum of HPE, emphasizing the need for comprehensive neurological assessment in affected individuals. The presence of an SMMCI is thus a significant indicator of potential midline developmental anomalies, including craniofacial anomalies, cognitive impairments, and other neurological troubles [2].

The genetic basis of SMMCI involves mutations that disrupt key developmental pathways governing midline patterning and organ development [5]. These mutations can lead to the variable expressivity observed in the syndrome, ranging from isolated dental anomalies to severe neurodevelopmental disorders. Therefore, early and accurate diagnosis is crucial not only for dental management but also for assessing potential neurological involvement.

The aim of this illustrated review is to provide a comprehensive update on the current knowledge surrounding SMMCI, exploring its etiopathogenic, clinical presentation, cone beam computed tomography (CBCT) presentation, examining the diagnostic criteria necessary to differentiate SMMCI from similar conditions, and reviewing current management strategies.

## Etiopathogenesis

The etiopathogenesis of SMMCI remains complex, and is subject to ongoing research. Several hypotheses have been advanced to elucidate the mechanisms underlying the development of SMMCI. The predominant theory, by Hall et al. in 1997, postulates that SMMCI results from a developmental anomaly occurring between the 35th and 38th days of gestation [3]. This critical period involves substantial morphogenesis of midline facial structures, including the maxilla and dental lamina, which are notably disrupted in SMMCI cases [3].

During this gestational window, the maxillary dental lamina begins to form, but an unexplained interruption or retardation of growth in the maxillary, orbital, and other midline structures is observed [3]. This disruption leads to the premature fusion of the right and left dental laminae and their corresponding dental buds [3, 6]. As a

result, the normal bifurcation into two distinct central incisor germs does not occur, thereby affecting the formation of the central incisors, as well as the surrounding bone and soft tissues [3, 6].

Current investigations are focused on identifying the genetic and environmental contributors to SMMCI. Noteworthy findings from research conducted by Li et al. indicate that mutations in the Sonic Hedgehog (SHH) gene, located on chromosome 7, are implicated in approximately 41.7% of SMMCI cases [5]. This gene plays a crucial role in the developmental processes of the face and brain [5]. Furthermore, genetic variants in other genes such as SIX3, TGIF1, COL4A2, DISP1, ZIC2, PTCH1, ASXL1, SMO, PLD2, and P2RY13 have been identified in individuals with SMMCI, suggesting a multi-factorial genetic basis for the syndrome [5].

Additionally, other studies have reported various chromosomal abnormalities associated with SMMCI, including deletions on chromosomes 18p, 22q11, and 2q21.2, as well as duplications on chromosome 20p12.1 and deletions on 15p [6-9]. These findings further complicate the genotype-phenotype correlations in SMMCI. The relationship between these genetic variants and the clinical manifestation of SMMCI is still under investigation, highlighting the need for more detailed genetic studies to understand the pathogenic pathways involved in this syndrome.

## Clinical presentation

SMMCI is characterized by the presence of a single, symmetrically positioned upper central incisor on the midline, observable in both deciduous and permanent dentitions, indicative of a mild variant within the HPE spectrum (Figure 1) [2, 4]. HPE, a developmental disorder, stems from the incomplete separation of midline structures during the 18th to 28th days of gestation [10]. It presents a spectrum of clinical manifestations, from severe, non-viable forms like alobar HPE with no cerebral hemisphere separation to milder lobular forms showing partial separation, particularly at the frontal cortex [10].

These brain malformations often co-occur with significant facial anomalies, including anophthalmia and hypotelorism [10]. While all patients with HPE exhibit SMMCI features, not all individuals with SMMCI have HPE, underscoring the variability in clinical expression [2]. Additionally, SMMCI may present alongside other complex syndromes such as CHARGE syndrome, VACTERL association, Goldenhar syndrome, velocardiofacial syndrome, ectodermal dysplasia, Duane retraction syndrome, type 1 oromandibular limb hypogenesis syndrome, DiGeorge syndrome, and Kabuki syndrome, each adding to the clinical complexity [2, 9, 11-14]. Given its autosomal hereditary nature, the genetic underpinnings of SMMCI, particularly its role in transmitting more severe forms of HPE, remains poorly understood, necessitating thorough genetic counseling and evaluation to assess and manage the associated risks.

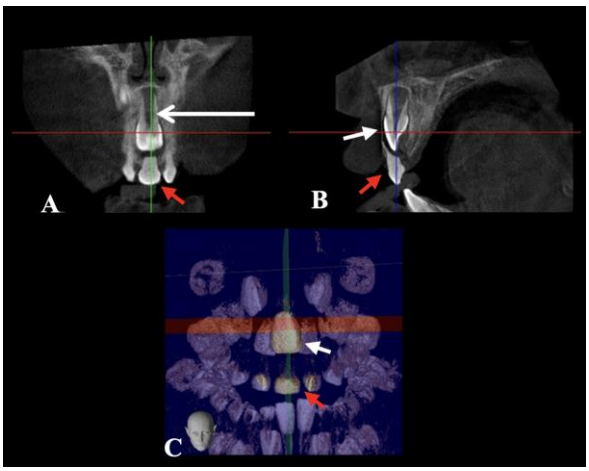


**Fig. 1. CBCT of a 6-year-old girl with SMMCI.** A. Coronal view B. Sagittal view. C. 3D reconstruction. Red arrows indicating the middle deciduous central incisor; white arrows indicating the middle permanent central incisor.

The various reported clinical characteristics that can be associated with SMMCI are summarized in Table 1.

**Table 1. Clinical manifestations associated with SMMCI.**

| Category | Features |
|---|---|
| Oral cavity | Absence of philtrum [2, 15] |
| | Elevated and arched upper lip (pseudo cleft appearance) [2] |
| | Absence of incisive papilla [2, 15, 16] |
| | V-shaped narrow palate [2, 15, 16] |
| | Absence of intermaxillary suture anterior to the incisive papilla [2, 17] |
| | Labial and/or palatine cleft [2, 18] |
| Craniofacial Characteristics | Reduced cranial circumference [2] |
| | Microcephaly [19] |
| | Hypotelorism [2] |
| | Ptosis [20] |
| | Narrow nasal bridge [2, 15] |
| | Choanal atresia [2, 21] |

| | |
|---|---|
| Neurocranial Malformations | Incomplete separation of cerebral hemispheres [2] |
| | Absence of the olfactory bulb [2] |
| | Agenesis of the corpus callosum [22] |
| | Abnormality of the sella turcica and pituitary morphology [23] |
| | Panhypopituitarism [24] |
| | Alopecia [20] |
| Systemic Manifestations | Premature birth [25] |
| | Intellectual disability [2, 26] |
| | Esophageal and duodenal atresia [2, 27] |
| | Congenital cardiac anomalies [2, 18] |

## Prenatal diagnosis

Prenatal screening for SMMCI primarily occurs during the 18th to 22nd weeks of gestation through routine ultrasound examination [2]. If midline anomalies suggestive of SMMCI or associated conditions like HPE are observed, further genetic testing may be warranted [2]. Chorionic villus sampling is recommended for detecting mutations in genes such as the SHH, which is frequently implicated in HPE [2]. While severe forms of HPE, characterized by significant structural brain anomalies, can typically be identified through these ultrasounds, microforms with more subtile features might be overlooked, as these may present a macroscopically normal brain appearance.

## Postnatal diagnosis

Postnatally, the diagnosis of SMMCI is established after birth, particularly when related physical manifestations such as respiratory distress from congenital anomalies like stenosis of the piriform aperture or choanal atresia are present [2]. In cases where SMMCI appears without additional syndromic features, the diagnosis is typically made by dental professionals. This often occurs between the ages of 1 to 9 years, coinciding with dental developmental milestones [2]. However, it can be detected as early as when the primary maxillary incisors erupt, around eight months of age.

## Differential diagnosis

Differentiating SMMCI from other conditions with similar presentations is critical. Possible differential diagnoses include:

1. Dental avulsion: Loss of one of the two central incisors can mimic the appearance of SMMCI but differs in that the remaining tooth is not centrally aligned. The incisor is then not symmetrical [2, 28],
2. Cell development anomaly: An anomaly in the development of one of the two central incisors may lead to dysmorphogenesis and premature cessation of cell differentiation, resulting in a solitary incisor [2, 28],
3. Tooth fusion: The fusion of a supernumerary tooth with either a permanent or primary central incisor may simulate the appearance of a single incisor but typically can be distinguished by detailed dental examination. [2, 28].

## Management and treatment planning

Once the diagnosis is made, it is important to refer the patient to an appropriate health facility to benefit from multidisciplinary care. This may involve specialists such as pediatricians to rule out other associated pathologies, ENT specialists in case of respiratory anomalies related to airway malformations, neuro-pediatricians to exclude brain malformations with the help of magnetic resonance imaging, endocrinologists in case of short stature for possible growth hormone treatment, and genetic counselors, as SMMCI is part of the HPE spectrum, and there is still an unknown risk of transmitting a more severe form of HPE to offspring [2, 28].
In the progression of age, dental treatment options may vary. For primary dentition, preventive care is predominantly sufficient [2]. Subsequently, the use of a space maintainer may become necessary prior to the placement of a fixed dental implant [2]. Alternative solutions include the replacement of missing teeth with either a removable prosthesis or a dental bridge [2]. In specific aesthetic cases, the extraction of a malformed tooth followed by the mesial movement and reshaping of adjacent lateral incisors and premolars might be indicated [2].

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- **Informed consent**: Patient was exempted from the informed consent according to the ethical committee approval.


### Authors contribution:

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| Maillet Alix | Conceptualization, Investigation, Writing original draft preparation, Writing review and editing |
| Issa Julien | Conceptualization, Investigation, Writing original draft preparation, Writing review and editing |
| Manzo Bruno | Resources, Validation, review and editing |
| Olszewski Raphael | Validation, Writing original draft preparation, Supervision, Writing review and editing |

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