**Abstract:**

Solitary median maxillary central incisor (SMMCI) is a rare syndrome, which can be associated with a combination of many developmental abnormalities. Sometimes it is related to background systemic features, but it may also be a separate localized anatomical aberration. It is estimated to have an occurrence of 1 per 50,000 live births and presents in both primary and permanent dentitions. SMMCIs have been described occurring in conjunction with cleft lip and palate (CLP), velo cardio facial syndrome (VCFS), exaggerated midline maxillary torus, distorted soft palate, and absence of the uvula and the midline labial frenum. Associated with systemic conditions, it has also been described with hypotelorism, hypothalamic-pituitary disorders, coloboma, ectodermal dysplasia and blindness secondary to microphthalmia. Nasal malformations such as flat nose with a single nostril, choanal atresia, mid-nasal stenosis, or congenital nasal pyriform aperture stenosis (CNPAS) can also occur concurrently with the disorder. In severe cases, it may be associated with holoprosencephaly (HPE) and cyclopia associated with Ito hypomelanosis. We present here occasional sporadic cases of otherwise normal children.

**Introduction:**

Solitary median maxillary central incisor (SMMCI) syndrome can be an isolated occurrence or part of a syndrome; either way it is a rare dental anomaly (1) with an incidence of around 1:50,000 live births (2). This anomaly is due to a heterozygous mutation in the Sonic Hedgehog Gene (SHH; [600725](http://omim.org/entry/600725)) on chromosome 7q36. (3)

The awareness of this anomaly goes back to 1958, when Scott described this syndrome in his paper entitled "Absence of upper central incisor" (3). Since then, the scientific literature regarding SMMCI has been characterized by single or sporadic case reports, as well as efforts to investigate the etiology and delineate associated developmental and genetic aberrations.

Patients with solitary maxillary central incisors in the primary and consecutive permanent dentitions have also been reported to have short stature and be growth hormone deficient. In some of these cases, growth hormone levels were normal. No similar or associated oral or dental aberrations were found in families of these patients. This phenomenon is termed superoincisivodontic dwarfism or monosuperoincisivodontic dwarfism (4,5). Choanal atresia/midnasal stenosis and holoprosencephaly (HPE) were described in addition to short stature in the report of 21 consecutive cases of SMMCI syndrome from 1966 to 1997 (2).

The holoprocencephaly spectrum (HPE) is a teratologic series of varying severity, expressed by median malformations of the face and brain. There are a variety of chromosomal causes, yet most cases are sporadic and of unknown etiology. Less severe cases of autosomal dominant HPE may present with mild manifestations of hypotelorism, anosmia, hyposmia (reduced ability to smell), microcephaly, mental deficiency, or midface hypoplasia, and SMMCI. Ocular colobomas may also be included.

HPE is a specific malformation complex caused by incorrect cleavage of the embryonic prosencephalon (forebrain). It has concurrent facial anomalies (midline facial structures) ranging from mild forms such as hypotelorism and SMMCI to cyclopia, with other clinical manifestations such as mild hypotelorism, coloboma, hyposmia, dysplasia of olfactory bulbs and optic nerves and even anophthalmia. (6)

The inheritance of HPE is autosomal dominant – the parents may present with minor manifestations such as single central incisor, hypotelorism, and hyposomia, but the offspring could have severe manifestations, which emphasizes the importance of genetic counseling.

While SMMCI syndrome was previously thought to be a simple midline defect of the dental lamina, it is now seen as "a possible predictor of HPEs of varying degrees in the proband, in members of the proband's family, and in the family's descendants" (2).

Although the majority of HPE cases occur sporadically, sometimes a single upper central incisor associated with HPE may be found in close relatives. These findings "may represent evidence for a less severe form of HPE that may be transmitted in an autosomal dominant fashion" (7).

Midline craniofacial malformations in association with hypothalamic-pituitary disorders were reported in a girl presenting with true precocious puberty and an SMMCI in both primary and permanent dentitions, and a hypothalamic hamartoma (8).

Genetics:

Genetic examination of two cases of SMMCI, one a 28-month-old boy (Dolan *et al*. 1981) and the other a 7 year old girl (Aughton *et al*. 1991), revealed that both had (18p) deletion syndrome (9,10). Due to the rarity of reporting of the anomaly at that time (1981-1991), the SMMCI were evaluated as fused maxillary central incisors. This syndrome is associated with a degree of HPE and in some cases with SMMCI as part of a mild manifestation of HPE (10).

Occasionally, SMMCI with semilobar HPE, a median cleft lip, flat nose with a single nostril, hypotelorism, and normal chromosomes, may be an incidental mutation in otherwise healthy close relative, with no obvious dental or facial anomalies. Indeed, the presence of SMMCI in a newborn baby suggests the need for genetic counseling as it is an indicator of potential HPE in the next generation, regardless of the fact that other relatives appear normal. The reason behind this suggestion is the wide range of penetrance and expression of the autosomal dominant form (11).

Winter *et al*. (1988) (12) and Buntinx and Baraitser (1989) (13) reported SMMCI in patients with a form of ectodermal dysplasia (ED). While this is an unusual manifestation of ED, it is significant as an indicator of possible gene carriers. The inheritance pattern in the family presented in these papers is likely to be autosomal recessive (AR) (12,13). Artman and Boyden (1990) (14) described a girl aged 5 years and one month who had 'slow growth', periodic severe headaches, intermittent nasal congestion, and was nearly blind secondary to microphthalmia. Both her height and weight were well below 3 standard deviations from the mean for her age and were at the 50th percentile for an 18 month and 9 month old child respectively. Her bone age was 2 years 5 months and a CT scan revealed a small sella turcica with a hypoplastic pituitary gland. She had a small bony ridge in the roof of her hard palate. Her growth hormone level was below that of normal controls. She was found to have microphthalmia and isolated growth hormone deficiency in association with SMMCI (14).

The association of SMMCI with nasal obstruction has been recognized (15). Brown (1989) reported congenital nasal pyriform aperture stenosis (CNPAS) as a cause of nasal airway obstruction in the newborn, but there was no mention of SMMCI (16).

SMMCI is a non-specific sign, since it occurs both as an isolated abnormality and as one aspect of HPE with autosomal dominant transmission (15). Patients suffering from CNPAS must be observed for eruption of an SMMCI, which has been described as ["megaincisor](file:///C%3A%5C%27megaincisor)" together with maxillary bony overgrowth. These patients should be assumed to have a microform of HPE, therefore should undergo chromosomal analysis, CT scan to check for CNS malformations, and assessment of the hypothalamic-pituitary-thyroid-adrenal axis. In addition, their parents should receive genetic counselling and other relatives should be evaluated. Indeed, CNPAS may suggest a midfacial dysostosis with associated endocrine and central nervous system abnormalities, and not just an isolated congenital abnormality of the airway.

SMMCI may occur as an isolated finding or in association with other systemic abnormalities such as short stature, pituitary insufficiency, microcephaly, choanal atresia, midnasal stenosis, and CNPAS. It can also be a feature of recognized syndromes with specific chromosomal abnormalities or have no chromosomal abnormality (17).

Masuno *et al*. (1990) (18) described two unrelated cases of SMMCI who had 7q terminal deletions. These patients presented with mental retardation, microcephaly, hypotelorism, short stature, and normal levels of plasma growth hormone. One patient had bilateral caudal ectopic kidneys, double renal pelvises, and dilated ureters. The other had bilateral hydroureteronephrosis. The authors suggested 7q terminal deletion as one of the causes of SMMCI (18).

In a molecular study of 13 patients with SMMCI who did not have HPE, Nanni *et al*. (2001) investigated two genes, SHH (600725) and SIX3 (603714), in which mutations had been reported in patients with SMMCI as part of the HPE spectrum (17). They found a new missense mutation in SHH (I111F; 600725.0014) that could be specific for the SMMCI phenotype since it had not been found in patients with HPE or in normal controls.

Marini et al. (2003) (19) studied a family that had been previously described by Camera et al. (1992) (20), in which the mother presented with an SMMCI and mild hypotelorism and the daughter and two fetuses were diagnosed with HPE. Marini sequenced the DNA in this family and identified a nonsense mutation in the SHH gene (19,20).

Here we present cases of otherwise healthy children with this phenomenon and one suspected to have systemic aberrations. About 30 years ago (1991), one of us (EM) came across a boy with SMMCI, which proved to be unfamiliar to most of our colleagues across the country (Figures 1 & 2) (21). At the present time, this case has two seemingly healthy children. Like his mother at the time, he currently refuses systemic or genetic examinations. A few more cases have been provided sporadically by practitioners. Only one additional child, with obvious features suggesting a syndrome (case EM), has been examined for dental treatment. The child’s mother refused further comprehensive examinations, which prevented the acquisition of detailed information. Hence, the purpose of this review and presentation of a further, small case series is to draw attention to the rarity of this phenomenon, sometimes referred to as a syndrome, or as part of a genetic feature with or without a variety of associated anomalies.

Case series

First two cases (Figures 1 & 2) were presented in detail in Mass and Sarnat 1991 (21).

Case no 3:

KS - A 7 year old boy was referred by a general practitioner for consultation, due to "Delayed dental development and a peculiar phenomenon in the maxillary incisal area". Other than the characteristic appearance in the primary and the following permanent SMMCI and exaggerated midline palatal torus in a maxillary cohesion, medical and dental examinations were inconclusive (Figure 3).

Case no 4:

EM - A 5 year old girl was referred for dental examination and treatment. The examination revealed a mid-nasal bulge; mild hypotelorism (in contrast, her brother had mild hypertelorism); atypical soft palate and lack of uvula; lack of anterior frenum; prominent mid palatal torus, without incisive papilla (Figure 4).

Upon suggestion to perform further systematic examination, the mother refused and left the clinic, claiming that she had brought the child for "fillings".

**Summary and Conclusions:**

**Background:** SMMCI and SMMCI syndrome are rare phenomena presented in the scientific literature only sporadically. Due to this rarity, it was felt that any additional reports may contribute to contemporary awareness of the importance of comprehensive case examinations.

**Aim**:

This article describes a case series of additional cases with common features, involving a solitary median maxillary central incisor. The patients were seen by different practicing dentists in Israel. Of these cases, none went through genetic and/or systemic examination, due to lack of awareness of its genetic and systemic implications, which otherwise were not noticed, and by refusal of one of the parents for further comprehensive examinations. However, we noticed two features, which have not been mentioned in previous reports, namely a tendency of the root apex of the SMMCI to split up and the lack of visible incisive papilla. Indeed, these two features are now recognized as possible predictors of holoprosencephalies of varying degrees in members of the proband's family, and in the family's descendants. Hence, it is hoped that this literature review and the presented cases will help to clarify our understanding of solitary median maxillary central incisor as a sporadic entity or as a syndrome, and prompt pediatric dentists to conduct thorough tests upon its detection.

**Conclusions:**

In a world of advanced technology and communications, any additional information has potential clinical significance and expands our understanding, which should improve our professional approach to the issue.

**List of figures**:

Figure 1. TA - (21) Anterior periapical radiograph: Note splitting of the pulp canal close to the apex (type IV according to Weine's classification (22)).

Figure 2. RM - Anterior periapical radiograph during orthodontic treatment (21). Note splitting of the pulp canal close to the apex (type IV according to Weine's classification (22)).

Figures 3. – Facial and dental clinical pictures and anterior periapical radiograph of case KS. Note the exaggerated midline palatal torus, lack of anterior labial frenum and incisive papilla.

Figure 4. – Facial and dental clinical pictures and anterior periapical radiograph of case EM. Note the exaggerated midline palatal torus, lack of anterior labial frenum, incisive papilla, posterior uvula with flabby soft palate.

REFERENCES:

1. Garavelli L, Zanacca C, Caselli G, Banchini G, Dubourg C, David V, et al. Solitary median maxillary central incisor syndrome: clinical case with a novel mutation of sonic hedgehog. Am J Med Genet 2004; 127A: 93-95.

2. Hall RK, Bankier A, Aldred MJ, Kan K, Lucas JO, Perks AGB. Solitary median maxillary central incisor, short stature, choanal atresia/midnasal stenosis (SMMCI) syndrome. Oral Surg Oral Med Oral Path Oral Radiol Endod 1997; 84: 651-662.

3. Scott DC. Absence of upper central incisor. Br Dent J 1958; 104: 247–248.

Online Mendelian In Men (OMIM **#** 147250).

4. Rappaport EB, Ulstrom RA, Gorlin RJ. Monosuperocentroincisivodontic dwarfism. Birth Defects Orig Art Ser 1976; XII(5 ) :243-245.

5. Rappaport EB, Ulstrom RA, Gorlin RJ, Lucky AW, Colle E, Miser J. Solitary maxillary central incisor and short stature. J Pediat 1977; 91: 924-928.

6. Liberfarb RM, Abdo OP, Pruett RC. Ocular coloboma associated with a solitary maxillary central incisor and growth failure: manifestations of holoprosencephaly. Ann Ophthal 1987; 19: 226-227.

7. Berry SA, Pierpont ME, Gorlin RJ. Single central incisor in familial holoprosencephaly. 1984; J Pediat 104: 877-880.

8. Winter WE, Rosenbloom AL, MacLean NK, Mickle PJ. Solitary, central, maxillary incisor associated with precocious puberty and hypothalamic hamartoma. J Pediat 1982; 101: 965-967.

9. Dolan LM, Willson K, Wilson WG. 18p- syndrome with a single central maxillary incisor. J Med Genet 1981; 18: 396-398.

10. Aughton DJ, AlSaadi AA, Transue DJ. Single maxillary central incisor in a girl with del(18p) syndrome. J Med Genet 1991; 28: 530-532.

11. Hattori H, Okuno T, Momoi T, Kataoka K, Mikawa H, Shiota K. Single central maxillary incisor and holoprosencephaly. Am J Med Genet 1987; 28: 483-487 [PubMed: 3425622, related citations]

12. Winter RM, MacDermot KD, Hill FJ. Sparse hair, short stature, hypoplastic thumbs, single upper central incisor and abnormal skin pigmentation: a possible 'new' form of ectodermal dysplasia. Am J Med Genet 1988; 29: 209-216.

13. Buntinx I, Baraitser MA. Single maxillary incisor as a manifestation of an ectodermal dysplasia. J Med Genet 1989; 26: 648-651.

14. Artman HG, Boyden E. Microphthalmia with single central incisor and hypopituitarism. J Med Genet 1990; 27: 192-193.

15. Arlis H, Ward RF. Congenital nasal pyriform aperture stenosis: isolated abnormality vs developmental field defect. Arch Otolaryng Head Neck Surg. 1992; 118: 989-991.

16. BrownOE, Myer III CM, Manning SC. Congenital nasal pyriform aperture stenosis**.** Laringoscope 1989; 99: 86-91.

17. Nanni L, Ming JE, Du Y, Hall RK, Aldred M, Bankier A, Muenke M. SHH mutation is associated with solitary median maxillary central incisor: a study of 13 patients and review of the literature. Am J Med Genet 2001; 102: 1-10.

18. Masuno M, Fukushima Y, Sugio Y, Ikeda M, Kuroki Y. Two unrelated cases of single maxillary central incisor with 7q terminal deletion. Jpn J Hum Genet 1990; 35: 311-317.

19. Marini M, Cusano R, De Biasio P, Caroli F, Lerone M, Silengo M, Ravazzolo R, Seri M, Camera G. Previously undescribed nonsense mutation in SHH caused autosomal dominant holoprosencephaly with wide intrafamilial variability. Am J Med Genet 2003; 117A: 112-115.

20. Camera G, Bovone S, Zucchinetti P, Pozzolo S, Giunta E. Incisivo mascellare centrale unico e eolprosencefalia. Pathologica 1992; 84: 425-428.

 21. Mass E, Sarnar H. Single maxillary central incisor in the midline. J Dent Child; Sep. Oct. 1991, 413-416.

22. Weine FS, Healey HJ, Gerskin H, Evanson L.Canal configuration in the mesibuccal root of maxillary first molar and its endodontic significance. Oral Surge Oral Med Oral Pathol 1969; 28: 419-425.