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REVIEW

WILEY PRENATAL DIAGNOSIS

The solitary median maxillary central incisor (SMMCI) syndrome: Associations, prenatal diagnosis, and outcomes

Raquel Garcia Rodriguez[1] | Loida Garcia Cruz[2] | Yeray Novoa Medina[3] | Raquel Garcia Delgado[1] | Julio Perez Gonzalez[4] | Carmen Palma Milla[5] | Juan Lopez Siles[5] | Margarita Medina Castellano[1] | Jose Angel Garcia Hernandez[1] | Alfredo Santana Rodriguez[2]

[1] Prenatal Diagnosis and Fetal Medicine Unit, Obstetrics and Gynecology Service, Complejo Hospitalario Universitario Insular Materno Infantil de Canarias, Las Palmas, Spain

[2] Clinical Genetics Unit, Complejo Hospitalario Universitario Insular Materno Infantil de Canarias, Las Palmas, Spain

[3] Pediatric Endocrinology Unit, Complejo Hospitalario Universitario Insular Materno Infantil de Canarias, Las Palmas, Spain

[4] Radiodiagnosis Service, Complejo Hospitalario Universitario Insular Materno Infantil de Canarias, Las Palmas, Spain

[5] Molecular Genetics Center GENETAQ. Institute of Genomic Medicine, MGC Genetaq, Málaga, Spain

Correspondence
Raquel Garcia Rodriguez, Prenatal Diagnosis and Fetal Medicine Unit, Obstetrics and Gynecology Service, Complejo Hospitalario Universitario Insular Materno Infantil de Canarias, Avda Marítima del Sur, sn, 35016 Las Palmas de Gran Canaria.
Email: raquelgarciarod@gmail.com

Abstract

Solitary median maxillary central incisor (SMMCI) syndrome is a complex disorder consisting of multiple, developmental defects involving midline structures of the head, which includes the cranial bones, the maxilla, and its container dentition (specifically the central incisor tooth germ), together with other midline structures of the body. SMMCI may appear as an isolated trait or in association with other midline developmental anomalies. We describe the case of a patient with SMMCI. He presented with a solitary median maxillary incisor, short stature, corpus callosum anomalies and a microform of holoprosencephaly (HPE), diabetes insipidus, and neurodevelopmental delay. The diagnosis was performed postnatally based on clinical features, radiological imaging, and a comprehensive genetic study. SMMCI can be diagnosed during the prenatal or neonatal periods or during infancy. Evaluation of the superior maxillary bone is important for prenatal diagnosis. Direct evaluation through bidimensional ultrasound or the use of multiplanar ultrasound or tridimensional reconstruction should be performed in cases of brain or face malformations. Early diagnosis can contribute to improved prenatal assessment and postnatal management.

1 | INTRODUCTION

Solitary median maxillary central incisor (SMMCI) is a rare dental anomaly that has been described as an isolated dental finding[1] or as part of the so-called "SMMCI syndrome" (OMIM#147250). SMMCI syndrome is a complex developmental disorder, involving neurodevelopment defects of the midline structures.

The development defects are determined by unknown factors operating in utero from the 35th to 38th day after conception, involving cranial bones, maxillary bone (SMMCI), airways (choanal atresia, midnasal stenosis, and nasal pyriform aperture stenosis), and midline brain structures.[2]

The estimated incidence of SMMCI syndrome is 1:50 000 live births,[3] in contrast to the other major traits present in this syndrome, namely, choanal atresia (incidence of 1:5000 live births[4]) and holoprosencephaly (HPE) (1:16 000 live births[5]).

We performed a literature review of SMMCI searching MedLine database and describe the typical and atypical presentations of these condition. We also describe an atypical case of SMMCI associated with corpus callosum agenesis.

2 | CLINICAL AND GENETIC ASPECTS

SMMCI is the mildest manifestation of the HPE spectrum. HPE is the most common structural anomaly of the developing forebrain, resulting from incomplete midline cleavage of the prosencephalon and associated with neurologic impairment and dysmorphism of the

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brain and face. HPE is classically divided into four types based on the degree of nonseparation of the prosencephalon.[6,7] These types in order of increasing cortical separation include the alobar form, characterized by diffuse cortical nonseparation; the semilobar form, characterized by nonseparation of the frontal lobes; the lobar form, characterized by nonseparation of the basal aspect of the frontal lobes; and the middle interhemispheric variant, characterized by nonseparation of the posterior frontal and parietal lobes.[8] Finally, very mildly affected "microforms" have been described wherein individuals may display subtle craniofacial features including microcephaly, hypotelorism (closely spaced eyes), and single maxillary central incisor but typically do not demonstrate obvious radiological evidence of nonseparation or severe neurological impairment.[9] The etiology of HPE is heterogeneous including genetic and environmental factors.[10]

Common congenital anomalies associated with SMMCI are the following: severe to mild intellectual disability, congenital heart disease, cleft lip and/or palate and less frequently, microcephaly, hypopituitarism, hypotelorism, convergent strabismus, esophageal and duodenal atresia, cervical hemivertebrae, cervical dermoid, hypothyroidism, scoliosis, absent kidney, micropenis, and ambiguous genitalia. Short stature is present in half the children.[11]

SMMCI syndrome has an autosomal condition inheritance; however, its reported genetic etiologies are very heterogeneous.[12] It is caused, primarily, by heterozygous mutations in the Sonic hedgehog gene[13] (*SHH*) on chromosome 7q36. *SHH* encodes a protein that is instrumental in patterning the early embryo. The Hedgehog (Hh) signaling pathway is crucial in the development of all animals. In the embryo, it regulates morphogenesis of a variety of tissues and organs; it has been implicated as the key inductive signal in patterning of the ventral neural tube, the anterior-posterior limb axis, and the ventral somites. In the adult, it controls stem cell proliferation. Defects on SHH protein or in its signaling pathway are related not only to HPE and SMMCI but also to VACTERL syndrome.

Fused central incisors are a feature of certain chromosome anomalies such as 18p-, del (18p), or del (7q).[14-16] Additionally, there have been chromosomal abnormalities described in association with SMMCI: *del(18p)*, *r (18)*, *(47,XXX)*, *(47,XXY)*, *(22q11.2 del)*, *(46,XX*, *del (6))*, (46,XX/47,XX, +9), among others.[12]

In regard to genotypic variation, furthermore, Nanni et al[12] found 36 different genetic variants in seven different genes: *SHH* gene (77%), *SIX3* (8.3%), *TGIF1* (2.7%), *GLI2* (2.7%), *PTCH1* (2.7%), *SALL4* (2%), and *FGF8* (2.7%).

Agenesis of the corpus callosum (ACC) is among the most frequent human brain malformations with an incidence of 0.5 to 70 in 10 000. It is a heterogeneous condition, which can be observed either as an isolated condition or as part of a congenital syndrome. The association of SMMCI with ACC has never been reported before.

What's already known about this topic?

- Solitary median maxillary central incisor (SMMCI) syndrome is a complex disorder consisting of multiple, developmental defects involving midline structures of the head, which includes the cranial bones, the maxilla, and its container dentition (specifically the central incisor tooth germ), together with other midline structures of the body. The SMMCI may appear as an isolated trait or in association with other midline developmental anomalies.

What does this study add?

- The association of corpus callosum agenesis and SMMCI is extremely rare and has never been reported before.
- SMMCI can be diagnosed during the prenatal or neonatal periods or during infancy. Evaluation of the superior maxillary bone is important for prenatal diagnosis. Direct evaluation through bidimensional ultrasound or the use of multiplanar ultrasound or tridimensional reconstruction should be performed in cases of brain or face malformations. Early diagnosis can contribute to improved prenatal assessment and postnatal management.

3 | CASE REPORT

We report the case of an infant born to a 23-year-old mother, without any past relevant personal or family diseases. On routine ultrasound performed at week 21 + 2, we found a male fetus with normal fetal biometry for his gestational age, bilateral colpocephaly with a ventricular atrium of 8 mm without visualization of the corpus callosum nor pericallosal artery. He was diagnosed at that time with complete corpus callosum agenesis. These findings led us to recommend fetal karyotype, which was not performed because of lack of maternal authorization. Maternal serology was undertaken to rule out TORCH infections; these results were negative. During follow-up, fetal biometry remained normal, with a persistent minor colpocephaly; a triangular image in the midline, located near the cavum septum pellucidum and a small tent-shaped separation of the interhemispheric line (Figure 1A). Mild polyhydramnios was noted to be present throughout gestation. In the three-dimensional (3-D) reconstruction of the fetal face, the eyelids seemed thick, and the nose was prominent with anteverted nostrils and a large mouth. Fetal magnetic resonance imaging (MRI) was performed at 28 weeks of gestation and confirmed the ultrasound findings; however, the upper maxilla analysis was not performed and was not studied at that time.

The child was born at a gestational age of 41 weeks, weighing 2930 g and measuring 46 cm. Cranial perimeter at birth was in 12th percentile, Apgar scores were 9.9, and umbilical artery pH was 7.26. Upon physical examination, he presented a small face, normal ears, hypertrophy of central-superior maxillary bone, ogival palate, partial stenosis of the left choana, and bilateral coloboma of iris and retina. Neurological exam was normal at the time of birth.

At age 53 days, he presented with vomiting. A blood analysis showed the presence of marked hypernatremia. After testing blood

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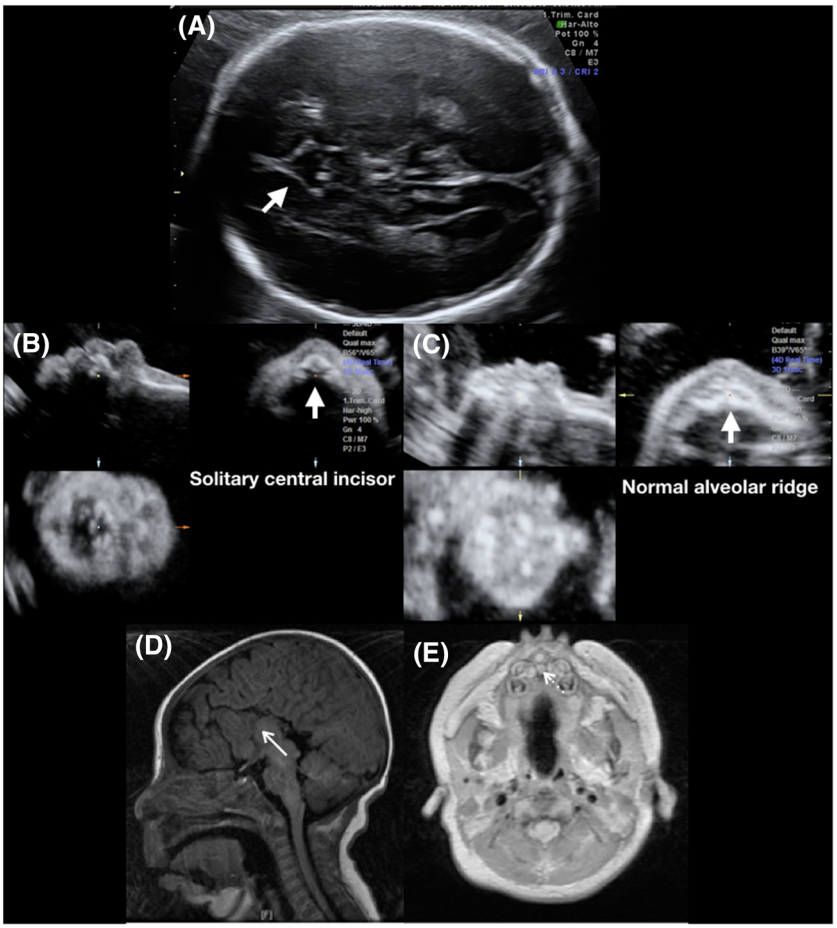

FIGURE 1 A, Fetal ultrasound examination at 27 + 4 wk of gestation of the case described in the main text. In axial planes, the cavum septum pellucidum is absent (arrow). B, Volumetric analyze archived in the database of the patient. The maxilla presents an abnormal alveolar ridge with a solitary central incisor. C, Volumetric analyses of a normal fetus with normal alveolar ridge. D, Postnatal MRI. In sagittal T1-weighted image, the corpus callosum is absent (arrow), abnormal profile with micrognathia. E, Magnet Resonance (RM) axial T1-weighted (three-dimensional gradient dual echo) axial T1-weighted images only a central incisor is present (dotted arrow). MRI, magnetic resonance imaging [Colour figure can be viewed at wileyonlinelibrary.com]

and urine samples, central diabetes insipidus was diagnosed. The patient was treated with intranasal dDAVP (desmopressin), achieving good control of the serum sodium values, osmolality, and daily diuresis.

He developed epilepsy, which was treated with clonazepam, vigabatrin, and valproic acid, and mild generalized hypotonia. At age 10 months, he showed a solitary central incisor and microcephaly. After these findings were reported, prenatal ultrasounds were rechecked, and the presence of a solitary central incisor orifice was found (Figure 1B). We compared this finding with a normal fetus (Figure 1C). The same finding was confirmed on the fetal MRI (Figure 1D). At 16 months of age, he was diagnosed with developmental and language delay. He presented with frequent bronchospasms and rhinitis requiring multiple visits to the pediatric emergency service and admissions to the hospital. He is currently under treatment in the pneumology department.

No adrenal, thyroid, or growth defects were found until age 20 months. At that time, his weight and height percentiles fell, from P50 to P3 in height and below P3 in weight, while maintaining normal serum sodium and osmolarity values at all times. Studies showed normal thyroid and corticotropin function, negative antitransglutaminase IgA, and normal IGF1 and BP3 values. Growth hormone (GH) stimulation tests revealed GH deficiency. He presented normal genital development, with both testes in the scrotum and normal penile length.

The karyotype was 46,XY. Genetic analysis on the patient's DNA was performed through massive sequencing of coding and intronic flanking regions using a panel containing 144 genes associated with HPE. To summarize, after generating libraries and enrichment (True Sight One, Illumina), paired end sequencing was performed (NextSeq, Illumina) obtaining a medium coverage of 132X. Variants were generated after alignment against the reference genome (hg19).

We identified five heterozygous variants of uncertain clinical significance in genes *DISP1* (c.4049delC), *ZIC2* (c.80C > T), *PTCH1* (c.109G > T), *SIX3* (c.514G > A), and *ASLX1* (c.583G > A) (Table 1). Genetic analysis of the parents ruled out de novo appearance of each of these variants. *SIX3* and *ASXL1* variants were inherited from his father and the *ZIC2*, *PTCH1*, and *DIPS1* from his mother.

Mutation Taster predicts "probably damaging" for all the five variants; four (of the eight predictors used) classify the *PTCH1* and *SIX3* variants as deleterious (Table 1). Other genes that have been involved in the process of odontogenesis (*SHH*, *TGIFI*, *GLI2*, *SALL4*, and *FGF8*) were not altered in our patient.

The patient is currently 30 months old and managed by a multidisciplinary team (endocrinology, neurology, pneumology, gastroenterology, and rehabilitation).

4 | DISCUSSION

There are many cases of SMMCI described in the literature, ranging from mild forms of HPE to more severe anomalies, with varied genetic

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TABLE 1 List of variants detected and bioinformatic prediction of pathogenicity

Gene	Cytoband	DNA Change	Aminoacide Change	SIFT	PolyPhen	LRT	Mut Taster	Mut Assesor	FATHMM	Radial SVM	LR_pred
DISP1	1q41	c.4049delC[a]	p.S1350fs	-	-	-	D	-	-	-	-
ZIC2	13q32.3	c.80C > T	p.A27V	T	P	D	D	N	T	T	T
PTCH1	9q22.32	c.109G > T	p.G37W	T	B	U	D	L	D	D	D
SIX3	2p21	c.514G > A[a]	p.A172T	D	P	U	D	M	D	D	D
ASLX1	20q11.21	c.583G > A[a]	p.A195T	T	D	D	D	L	T	T	T

Note. Complete description of the five variants detected in our patient: gene affected, cytoband, DNA, ammoniated changes, and bioinformatic prediction (SIFT, PolyPhen, LRT, Mutation Taster, Mutation Assesor, FATHMM, Radial SVM, and LR_pred).

Abbreviations: B, benign; D, deleterious; L, low risk; M, medium risk; N, neutral; P, polimorphism; T, tolerated; U, unknown.

[a]Variants not previously described.

bases. Prenatal diagnosis is possible, as shown by Johnson et al,[16] who published the case of a fetus with semilobar HPE and SMMCI who was diagnosed prenatally with an MRI. To our knowledge, we describe the first case of a patient presenting with agenesis of the corpus callosum along with the corresponding prenatal ultrasound images.

The use of the midsagittal plane facilitates the detection of facial anomalies, as well as profile evaluation and measurement of some parameters such facial angles and nasal bones. The axial views of the face, enable facial examination and series of transverse views from the top of the head moving caudally, allow examination of the forehead, nasal bridge, orbits, nose, upper lip and anterior palate, maxilla and alveolar ridge, the tongue within the oral cavity, and lower lip and mandible (Figure 2). We use the bidimentional ultrasound to explore the fetal upper maxilla. In our case, the stored volumetric acquisition of the fetal face allowed the off-line study of the fetal abnormalities detected postnatally. The use of 3-D ultrasound offers a true anatomical view of the fetal palate, hard and soft palate, that it is difficult to assess by bidimentional ultrasound.[17] The evaluation of dental alveoli and germinal teeth by prenatal ultrasound in fetuses with midline pathology may contribute to the identification of SMMCI and raise the suspicion regarding the presence of associated genetic syndromes.

In our department, we have added the routine examination of the fetal palate, maxilla and the incisors (Figure 2), and we consider visualization of the superior maxillary bone as part of the fetal ultrasound examination in fetuses with brain or face malformations.

With respects to the genetic analysis of our patient, globally, we detected five genetic variants in five different genes. Variants were inherited from asymptomatic parents so, given the autosomal dominant inheritance of SMMCI, it is not possible to establish a clear genetic diagnosis. We found that, in relationship to *DISP1* gene, there is a previous description of a case involving microform of HPE with a similar mutation without clear segregation.[18] Similarly to what we found in our patient, the mutation was inherited from an asymptomatic mother. In our case, we ruled out the possibility of the mother's presenting with mosaicism. We find it likely that *DISP1* gene is a susceptibility gene, probably as part of a more complex model.

Recommendations for making the diagnosis of SSMCI prenatally are based upon assessment of the fetal head, face, nose, eyes, mouth, and palate. In the case of midline anomalies such as agenesis of the corpus callosum, HPE, facial fissures, micrognatias, or other craniofacial anomalies, the superior maxillary should be assessed either directly with two-dimensional ultrasound or through the use of multiplanar ultrasound or 3-D reconstruction. In neonates, the diagnosis should be suspected in the case of children with narrow choanae and nasal obstruction, in those with prominent upper jaw, arched palate and/or absence of lingual frenulum. If there is any degree of

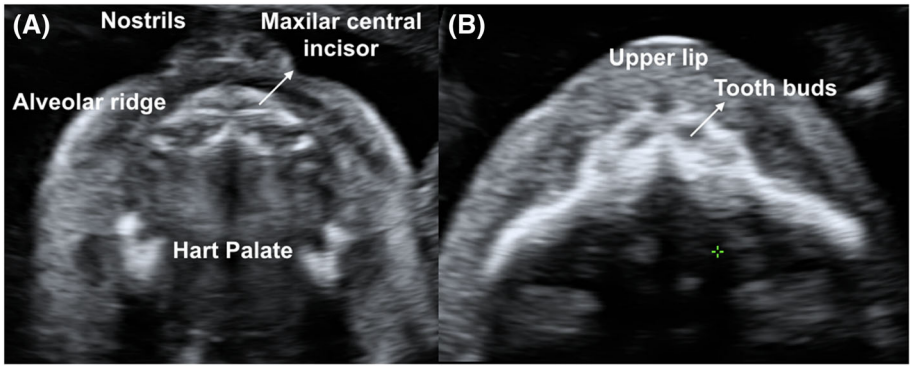

FIGURE 2 Normal fetus two-dimensional (2-D) ultrasound image of the maxilla at 22 weeks gestation. To obtain a better visualization, the fetal head must be deflected. The maxilla appears as a regular, U-shaped echoic structure (A). The alveolus and tooth buds appears hypoechoic regularly layered along the alveolar ridge (B). In the anterior part appears the maxillary central incisors. The anterior part of the hard palate is semicircular and lies immediately posterior to the alveolar ridge [Colour figure can be viewed at wileyonlinelibrary.com]

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hypotelorism, SSMCI should be considered in association with HPE and its different variants.

A multidisciplinary approach with pediatricians, neurologists, endocrinologists, geneticists, and dentists is necessary for the adequate management of these children. Molecular diagnosis and genetic counseling are important in patients with SMMCI and their relatives.

FUNDING SOURCES

None

CONFLICTS OF INTEREST

None declared

ETHICS APPROVAL

We have the consent of the patient parents for images and other information relating to the case report, for consideration of publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Raquel Garcia Rodriguez https://orcid.org/0000-0003-4079-8152
Raquel Garcia Delgado https://orcid.org/0000-0002-8166-3644

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