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Case Report

# Combined Currarino Triad/Syndrome with SMMCI Syndrome and 7q 36 Deletion: A Case Study

*Atar M[1*], Koerperich EJ[2], Khalefa M[2] and Jost-Brinkmann PG[2]*

[1]*Department of Pediatric Dentistry, New York University NYU College of Dentistry, USA*

[2]*Department of Orthodontics, Dentofacial Orthopaedics and Paediatric Dentistry, Charité Universitätsmedizin Berlin Centre for Dental and Craniofacial Sciences, USA*

## Abstract

We report here the first documented case of SMMCI combined with Currarino Syndrome and holoprosencephaly. SMMCI may affect midline structures of the head, the nasal airways, the brain, and other midline structures of the body. Affected individuals can be carriers for HPE, which is a potentially more serious condition affecting midline development of the brain and face. Both conditions involve SHH at 7q36. CS is also linked to the 7q36 region but does not involve SHH. Anomalies in the 7q36 region of chromosome 7 are likely to be involved in the manifestation of SMMCI, HPE and CS in this patient. Appropriate genetic testing and counselling should be offered to patients diagnosed with SMMCI.

## Case Report and Differential Diagnosis

Our patient, L, was a male child of a healthy and non-consanguineous couple. The pregnancy was uneventful and the patient was born spontaneously out of cephalic presentation. At birth the mother was 32 years old and the father 37. L first presented to the Charité University Hospital, Berlin in 2004 at the age of 2 months following several epileptic and was subsequently treated with phenobarbital.

Subsequently the following craniofacial abnormalities, typical of holoprosencephaly (HPE), were noted: facial dysmorphism with microcephaly, small mouth, and retrognatism. In addition the patient was diagnosed with Currarino-associated anomalies (partial agenesis of the os sacrum, distal rectum, and anal stenosis and mass in the os sacrum), as well as recurrent respiratory insufficiency [1]. Tethered cord, patent foramen ovale PFO/ASD (arterial septal defect), extrarenal renal pelvis on the right side, and hypospadias were also observed. Chromosomal analysis revealed a deletion in the long arm of chromosome 7 (7q36). Because of the deformity in the lumbosacral region L was placed under the care of the social paediatric service.

The presence of a solitary symmetrical maxillary central incisor of normal crown dimensions, situated precisely in the midline in both primary and permanent dentitions was first reported by Scott in 1958. The name solitary median maxillary central incisor (SMMCI) was originally given to this syndrome by Hall [2-6].

SMMCI syndrome (phenotype) is a rare, unique developmental abnormality of uncertain aetiology with an estimated frequency of 1:50,000 live births. It occurs as a result of unknown factors operating in utero between the 35th and 38th days post-conception. The syndrome affects midline structures of the head including the cranial bones, the maxilla and its contained dentition (specifically the central incisor tooth germs), and the nasal airways (choanal atresia, midnasal stenosis or congenital pyriform aperture stenosis), and sometimes the brain (holoprosencephaly, HPE). Other midline structures of the body may also be involved [7,8].

Unlike the normal central incisor, the crown form of the SMMCI tooth is symmetric; the tooth develops and erupts precisely in the midline of the maxillary dental arch in both primary and permanent dentitions. The eruption time of the single central incisor in children with SMMCI is normal; however, the intermaxillary suture in the incisor region is abnormal. This interincisal midline defect does not appear to influence the eruption pattern.

SMMCI subjects have a characteristic external nose, an arch-shaped upper lip, and an indistinct phlitrum; intraorally they lack the fraenulum of the upper lip and the incisive papilla; most subjects have a characteristic midaxial ridge in the palate. Patients have a short anterior cranial base, and most have a retrognathic maxilla [9].

Several associated developmental disorders have been described, such as short stature, pituitary and endocrinological deficiencies, brain malformation and mental retardation (which varies from severe to mild), microcephaly, hypotelorism, convergent strabismus, congenital nasal pyriform aperture stenosis (CNPAS), chonal atresia, a midpalatal ridge, and VACTERL association (vertebral anomalies, anal atresia, tracheooesophageal fistula, renal defects, and limb dysplasia), micropenis and ambiguous genitalia.

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***Corresponding author:** Michael Atar, Department of Pediatric Dentistry, New York University NYU College of Dentistry, USA, E-mail: atardrs@yahoo.com

The first report of a chromosome defect in children with SMMCI came from Dolan in 1981, who found a deletion on the short arm of chromosome 18 (18p-). The chromosome abnormalities thus far described in the literature associated with SMMCI are those involving chromosomes 7 [del(7q36 ter)], 18 [del(18p) and r(18)], 22 [del(22q11.2)] and 47 [47XXX]. SHH missense mutations I111F {Nanni, 2001 #24} and Val332Ala {Garavelli, 2004 #23} have also been associated with SMMCI. The relevance of the association of SMMCI with the syndromes and chromosome anomalies described above remains to be elucidated [10].

Holoprosencephaly (HPE) is a complex developmental defect of the forebrain in which the cerebral hemispheres fail to separate into distinct halves. The basic defect in HPE is an impaired midline formation of the embryogenic face and forebrain, and exhibits a wide phenotypic variation. It is estimated to occur at or before Streeter Horizon XV (days 35–37 in utero) at a frequency approximately 1 per 16,000 live births. HPE is classified into alobar, semilobar and lobar, indicating the degree of the division of the brain hemispheres, with the alobar form being the most severe form. Facial anomalies vary from the least severe median cleft lip (premaxillary agenesis) to the most severe cyclopia.

The known HPE genes are SHH at 7q36, ZIC2 at 13q32, SIX3 at 2p21 and TGIF at 18p11.3. The SHH gene at 7q36 has been identified as the HPE3 locus. Nanni suggest that missense mutation in the SHH gene (I111F) at 7q36 may be specific for the SMMCI phenotype as it has not been found in the HPE population they studied or in normal controls. SHH mutations are associated with a broad spectrum of cerebral midline defects. SHH also plays an important role in defining the anterior-posterior axis in the developing limbs [11-15].

The final phenotype for a given individual is dependent on the interactions of multiple gene products and/or environmental elements. Variations among these factors may cause the wide variability in the clinical features seen in HPE. Although in the majority of cases HPE does occur in the absence of SMMCI, the SMMCI tooth should be considered a predictor of HPE. SMMCI is not a microform of HPE. Several mechanisms which may be involved in the manifestation of SMMCI syndrome, may also cause HPE.

The Currarino syndrome (CS) is a relatively unknown hereditary disorder linked to the 7q36 region, the same region as SMMCI and holoprosencephaly (HPE3). Contrary to HPE, however, SHH is not thought to be involved in the pathogenesis of CS. CS is characterised by an anorectal malformation, sacrococcygeal defect, and a presacral mass. The phenotypical expression of the gene mutations causing the Currarino triad can vary from asymptomatic to patients presenting with the complete triad. DNA screening is the only method to fully exclude the triad [15-19].

Cleidocranial dysplasia (CCD) is an autosomal dominant skeletal disorder characterized by clavicular, pelvic and dental anomalies. It is caused by mutations in the osteoblast-specific transcription factor CBFA1/RUNX2 on 6p21. We reported elsewhere a first documented case of CCD (in conjunction with the presence of supernumerary teeth) with thyroid gland agenesis. Fernandez identified a case of CCD combined with premaxillary agenesis (which is part of the HPE spectrum). They suggest that the proband's complex phenotype is due to two position-effect (PE) mutations, one at each translocation breakpoint, which have altered the expression of the SHH and CBFA1/RUNX2 genes. Fluorescence in situ hybridization (FISH) studies indicate that in patients with subtle or submicroscopic 7q36 deletions, the SSH gene and the homeobox gene HLXB9, among others, are involved. Mutational analysis of the SHH gene should be considered in patients presenting with the classical HPE phenotype and in those with two or more clinical signs of the wide phenotypic spectrum of associated abnormalities, especially in combination with a positive family history. It has been suggested that patients with even minimal signs of HPE should be screened for 7q36 deletions. In addition, SMMCI syndrome cases and their relatives should be carefully investigated for related midline disorders, especially of the HPE spectrum, and all known HPE genes screened. {Dibiase, 2008 #20; El-Jaick, 2007 #21} SMMCI may be considered as an indicator of potential holoprosencephaly in the next generation.

Diagnosis of SMMCI is possible with ultrasound at 18–22 weeks gestation or, possibly, following genetic testing in familial cases, but is rarely carried out prenatally. With the present awareness of the condition, diagnosis should be made by 8 months of age on eruption of the primary maxillary incisor tooth.

## Discussion

This is the first documented case of SMMCI combined with CS and HPE. A previous case of CS with minimal manifestations of the HPE spectrum has been reported. Although trauma, or more rarely hypodontia, is the most common cause, SMMCI is also a recognised genetic anomaly associated with abnormalities in chromosomes 7, 18, 22 and 47 and occurring as a result of unknown factors operating in utero between the 35th and 38th days from conception [20]. SMMCI syndrome involves midline structures of the head including the cranial bones, the maxilla and its contained dentition (specifically the central incisor tooth germs), the nasal airways, and sometimes the brain, together with other midline structures of the body. Affected individuals (who may or may not have any other relevant clinical signs) can be carriers for HPE, which is a potentially more serious condition affecting midline development of the brain and face. The known HPE genes are SHH at 7q36 (HPE3), ZIC2 at 13q32, SIX3 at 2p21 and TGIF at 18p11.3 [21-24]. Thus appropriate genetic testing and counselling should be offered to patients diagnosed with SMMCI. Diagnosis of SMMCI should be made by eight months of age, although diagnosis is also possible at birth and in utero (at 18-22 weeks gestation). CS symptoms include anorectal malformation, sacrococcygeal defect, and a presacral mass. CS is a relatively unknown hereditary disorder linked to the 7q36 region, the same region as SMMCI and holoprosencephaly (HPE3), but does not involve SHH. We postulate that anomalies in the 7q36 region of chromosome 7 are likely to be responsible for the manifestation of SMMCI, HPE and CS in this patient. Although SHH is not thought to be implicated in CS, it is likely that more than one chromosomal defect at the 7q36 region may actually be involved [25-27]. Aesthetic management of SMMCI tooth ideally involves a combination of orthodontic, prosthodontic and oral surgical treatments, although in many cases SMMCI tooth is left untreated.

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