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## CASE REPORT

# DiGeorge Syndrome Associated with Solitary Median Maxillary Central Incisor

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**SUMMARY** DiGeorge syndrome is a primary immunodeficiency disease characterized by dysgenesis of the thymus and parathyroid glands, conotruncal cardiac anomalies, and other dysmorphic features. Although most patients have a common microscopic deletion in chromosome 22q11.2, marked clinical variability exists. A solitary median maxillary central incisor (SMMCI) is a rare dental anomaly which may be an isolated occurrence or associated with congenital nasal airway abnormalities or holoprosencephaly. We report a patient with DiGeorge syndrome who was diagnosed at nearly 1 month of age and was later found to have a solitary median central incisor. Initially, the patient presented with recurrent episodes of respiratory distress attributed to partial airway obstruction, one of the phenotypic features of SMMCI. A fluorescence *in situ* hybridization study showed a chromosome 22q11.2 deletion.

DiGeorge syndrome is the most common chromosomal deletion syndrome in humans, with a frequency in the general population of approximately 1:4,000.[1,2] It is characterized by a conotruncal cardiac anomaly, neonatal hypocalcemic tetany resulting from parathyroid gland dysgenesis, a hypoplastic thymus gland leading to congenital T cell immunodeficiency, and a number of dysmorphic features. It can be further divided into complete and partial forms according to the status of the cellular immunity.[3] The majority of cases (90% to 95%) are attributed to a submicroscopic deletion of chromosome 22q11.2. Since 1965 when it was first described, new features of DiGeorge syndrome continue to be reported.

Solitary median maxillary central incisor (SMMCI) is a rare anomaly of dental development. In most reports, SMMCI has been linked to holoprosencephaly or congenital nasal airway abnormalities. In 1997, Hall *et al.*[4] reported a case of SMMCI associated with velocardiofacial syndrome but did not discuss the possible developmental relationship between them. Here we present a patient with DiGeorge syndrome who also had an SMMCI. The possible relationship between DiGeorge syndrome

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and SMMCI is also discussed.

## CASE REPORT

A 23-day-old female patient was referred from another hospital with a history of intermittent respiratory distress since birth.

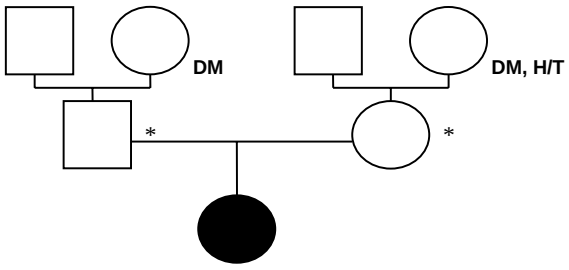
She was born uneventfully at another hospital at 41 weeks of gestation to a gravida 1 para 1 mother by vaginal delivery. On the second day of life, she began to have intermittent respiratory distress, retraction, and grunting, and was transferred to the hospital's neonatal intensive care unit. A sepsis workup was done and she was then treated with broad spectrum antibiotics. Another episode of cyanosis was noted 12 days later. A repeat workup for sepsis did not reveal any infection. She also had persistent hypocalcemia (total serum calcium: 5.9 to 7.5 mg/dl; ionized calcium: 2.1 to 2.4 mg/dl) and hyperphosphatemia (serum phosphorus: 9.3 to 9.8 mg/dl) despite a calcium gluconate infusion. She was transferred to our hospital after a third episode of respiratory distress and cyanosis on the 22nd day of life.

There was no maternal history of diabetes or hypertension, and the mother had no drug or alcohol exposure during pregnancy. The family tree is shown in Fig. 1.

On physical examination, the infant's weight was 2,762 gm, length 46 cm, and head circumference 33.5 cm. There was no fever but she had mild tachypnea. Grossly, she was acutely ill-looking. She had pseudo-low-set, notched ears and a short philtrum. There were suprasternal and subcostal retractions of the chest wall. On auscultation, she had stridor and mild rales bilaterally. No heart murmur was audible. The abdomen was mildly distended, the liver edge was 2 cm below the right costal margin, but the spleen was impalpable. There was a maculopapular rash on the face.

After admission, the patient was given $O_2$, had a sepsis workup, and was treated with empiric antibiotics. The hemoglobin was 11.3 mg/dl and packed red cells were immediately transfused. The WBC was 11100/cmm with a differential count of 1% bands, 60% segments, 15% basophils, 19% lymphocytes, 1% myelocytes, and 3% metamyelocytes. The chest x ray showed perihilar infiltrates bilaterally. There was no thymus shadow seen. Because we suspected DiGeorge syndrome, an immunologic survey was done which showed 48% T cells, 6% B cells, 37% CD3, 28% CD4, and 18% CD8 cells. Skin testing for delayed hypersensitivity using a multitest system (including tetanus toxoid, diphtheria toxoid, *Streptococcus*, *Proteus*, *Trichophyton*, *Candida*, tuberculin, and glycerin as a negative control) was uniformly negative. Echocardiography demonstrated no major conotruncal anomaly except for a small secundum atrial septal defect. The iPTH level was 27.11 pg/ml.

The patient continued to have intermittent tachypnea and stridor and remained oxygen dependent. Laryngoscopic examination showed no signs of laryngomalacia, but there was purulent discharge from the middle meatus in the nasal cavity. On the 18th day of admission, the infant had a sudden onset of severe tachypnea and respiratory distress. Arterial blood gas analysis showed $CO_2$ retention, whereupon she was transferred to the pediatric intensive care unit and intubated. A sepsis workup was repeated, followed by empiric treatment with ampicillin and gentamicin. Nasopharyngeal secretions were positive for respiratory syncytial virus antigen. Ribavirin inhalation therapy was therefore given for 3 consecutive days. The patient's condition improved and she was extubated 3 days later. Cultures of blood, urine and cerebrospinal fluid were all negative. She was discharged after 35 hospital days on oral calcitriol. A chromosome study using FISH analysis showed a




*The FISH studies of the parents are both normal.

DM, Diabetes mellitus; H/T, Hypertension

**Fig. 1** Family tree of the patient.

chromosome 22q11.2 deletion. (Fig. 2)

Several months later, a single primary incisor erupted in the maxillary alveolus. SMMCI syndrome was diagnosed.

The patient has been followed in our clinic for 11 years, and her immunologic status is nearly normal, although the T-cell count is always slightly lower than normal (CD3 55%, CD4 40%, CD8 26% at 6 months of age; CD3 37.4%, CD4 23.0%, CD8 11.2%, CD19 19.7%, CD57 11.2%, and active T cells 5.3% at 10 years of age). She has had only one other hospital admission for acute bronchiolitis when she was 6 months old. She took oral calcium carbonate irregularly, and the follow-up serum calcium was slightly lower than normal, but she was clinically eucalcemic. The secundum atrial septal defect closed spontaneously. She attended school at the appropriate age, although her school performance is poor. Results of intelligence testing were borderline (IQ = 85).

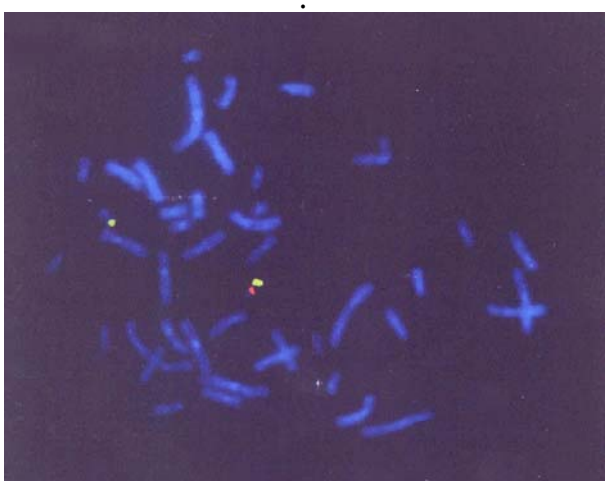


**Fig. 2** FISH study. The TUPLE 1 gene mapped to 22q11.2 was labeled with SpectrumOrange and the ARSA (arylsulfatase) gene mapped to 22q13 was labeled with SpectrumGreen which was used as the control probe. The FISH study showed that one of the TUPLE 1 genes is deleted.

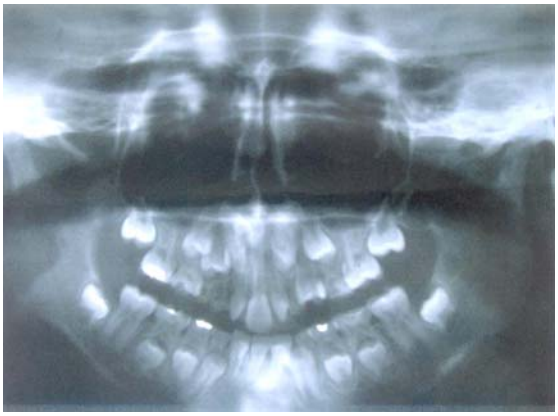


**Fig. 2** Orthopantomogram. Note the symmetrical single maxillary central incisor and the asymmetric septum deviated to the right.

## DISCUSSION

The chromosome 22q11.2 microdeletion seen in most patients with DiGeorge syndrome has also been found in patients with velocardiofacial syndrome or conotruncal anomaly face syndrome. Although the size and position of these chromosomal microdeletions may differ, more than 90% of patients with DiGeorge syndrome have the same 3 Mb deletion.[3,5-7] There are approximately 30 genes in this region, and several candidate genes, including *Tbx1*, *Crkol*, and UFD1L, have been implicated in various facets of the DiGeorge phenotype.

A striking aspect of the DiGeorge syndrome is the discordance between genotype and phenotype. There is no obvious correlation between the size or site of deletion and the severity of the clinical phenotype, as demonstrated, for instance, by the different phenotypes observed in monozygotic twins.[8] It is thought that other non-genetic factors may contribute to the phenotypic variability, either by affecting recovery from or by influencing the severity of an early embryonic defect.[7]

SMMCI (Online Mendelian Inheritance in Man, OMIM, #147250)[9] was first described by Scott in 1958.[10] It is a rare dental anomaly with an incidence of about 1 in 50,000 live births.[4] It may be an isolated anomaly or combined with other morphogenic defects, including hypotelorism, indistinct philtrum, arch-shaped upper lip, absence of the frenulum of the upper lip, vomerine ridge, and nasal obstruction or septal deviation.[11] Over 90% of cases are associated with one of three forms of congenital

nasal cavity abnormalities: choanal atresia, midnasal stenosis, or nasal pyriform aperture stenosis. However, the clinical significance of SMMCI lies in its association with holoprosencephaly, which is a lethal disorder when fully expressed. SMMCI itself has been thought to be the mildest form of holoprosencephaly.[12] The offspring of patients with isolated SMMCI are at risk for holoprosencephaly.[13-15] It is thought that the spectrum of disease (from isolated SMMCI to holoprosencephaly and the most extreme expression, cyclopia) results from a developmental anomaly of anterior midline structures.[4] Other features associated with SMMCI include short stature and variable degrees of intellectual disability.

To date, the exact genetic or pathogenic defect of SMMCI is undetermined. There is some evidence showing that isolated SMMCI can result from mutations in the Sonic hedgehog gene (*SHH*) on the long arm of chromosome 7.[16,17] It has also been reported as a part of syndromes with more severe midline defects, including the CHARGE and VACTERL associations and, rarely, the velocardiofacial syndrome.[18,19] Chromosome abnormalities, including chromosome 18p deletion, ring chromosome 18, chromosome 7q terminal deletion, and 47XXX, have also been described in case reports.[20-26] A chromosome 22q11.2 deletion with velocardiofacial syndrome and SMMCI has been reported once in a retrospective cohort study.[4] It is postulated that SMMCI is a developmental defect based on varying genetic abnormalities and related to the fusion,[27] germination,[28] or absence of the maxillary central incisor.[10]

Is there, then, an actual developmental relationship between the DiGeorge syndrome and SMMCI? While the answer remains uncertain, there do appear to be some connections between the two. First, both present as a spectrum of phenotypes and exhibit some overlapping features, including cleft palate, bifid uvula, cardiac anomalies, indistinct philtrum, and learning problems.[16] Second, from the point of view of embryology, the thymus and inferior parathyroid gland arise from the third pharyngeal pouch in the fifth week.[29] Similarly, the midfacial structures are induced when the prechordal mesoderm migrates forward into the area anterior to the notochord during the fifth week of gestation. If the process is defective, varying deficits of midline facial development occur.[30] It is postulated that the lateral growth of dental lamina from the midline is interfered with around the 35th to 38th day of gestation, resulting in premature fusion and thus the formation of single central incisor.[4,16] Because of the proximity in time of the development of the thymus and the midfacial structures, it is reasonable to infer that the same insult could result in both defects. In fact, recent animal models showed that *Tbx1* is regulated by the *SHH* gene during pharyngeal arch development,[31,32] thus further implying a relationship between DiGeorge syndrome and SMMCI.

In the past, the diagnosis of the DiGeorge syndrome was based on the characteristic clinical expression. However, molecular study with FISH now allows easy detection of chromosome 22q11.2 deletion. The diagnosis of SMMCI is relatively straightforward and depends on the finding of a solitary median primary central incisor tooth situated precisely in the midline of the maxillary alveolus. Early diagnosis of the condition in the newborn stage is possible by the recognition of a midline prominence of the maxillary alveolus. Congenital nasal cavity anomalies leading to life-threatening nasal airway obstruction may also provide a clue for early diagnosis.[33] In our patient, the repeated episodes of respiratory distress may be explained by a partial obstruction of the nasal airway caused by a septal deviation (Fig 3).

In summary, DiGeorge syndrome combined with SMMCI syndrome is extremely rare. Although there is still much to be learned about the relationship between DiGeorge syndrome and SMMCI, clarifying a developmental association between the two will be helpful in understanding the pathogenesis of these anomalies.

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