Solitary median maxillary central incisor, holoprosencephaly and congenital nasal pyriform aperture stenosis in a premature infant: case report

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ABSTRACT
Solitary median maxillary central incisor syndrome is a rare disorder involving midline abnormalities such as holoprosencephaly, nasal cavity anomalies, cleft palate-lip, hypotelorism, microcephaly, and panhypopituitarism. Congenital nasal pyriform aperture stenosis is a lethal cause of neonatal respiratory distress due to narrowing of the pyriform aperture anteriorly and it can be confused with choanal atresia. In this report, we present a newborn infant with solitary median maxillary central incisor syndrome accompanied by other abnormalities including holoprosencephaly, nasal pyriform aperture stenosis, microcephaly and panhypopituitarism. Chromosomal analysis showed heterozygous SIX3 gene deletion at 2p21 region resulting in a more severe form of holoprosencephaly.

Key words: Congenital nasal pyriform aperture stenosis, solitary median maxillary central incisor, holoprosencephaly, hypopituitarism, respiratory distress.

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INTRODUCTION
Solitary median maxillary central incisor (SMMCI) is a rare condition which can occur as an isolated dental anomaly, but it can also occur as a part of the SMMCI syndrome. It is a complex, autosomal dominant disorder; the incidence is 1/50,000 live births. This syndrome can be accompanied by midline field defects such as holoprosencephaly, nasal cavity anomalies, cleft palate-lip, hypotelorism, microcephaly, and panhypopituitarism. Premature delivery, low birth weight and growth retardation can be observed.

Herein, we report a newborn infant with SMMCI syndrome accompanied by other abnormalities such as holoprosencephaly, nasal pyriform aperture stenosis, microcephaly and panhypopituitarism.

Case report
The present case was born at 32 weeks of gestation via spontaneous vaginal delivery to a 30-year-old healthy mother by her fourth pregnancy and a 35-year-old father without consanguinity with the mother; birth weight was 1800 grams; the parents referred that the baby was intubated and connected to the mechanical ventilator at a private hospital due to choanal atresia and panhypopituitarism. After referral of the patient to our center at postnatal 64 days for further tests and continuation of treatment, the patient was admitted to the neonatal intensive care unit. On admission, her general condition was poor, she was intubated, blood pressure was 79/45 (56) mmHg, pulse rate was 130/min, body temperature was 36.4 °C, body weight was 2180 g (<3 p), height was 44 cm (<3 p), and head circumference was 28 cm (<3 p). The patient had hypotonia and microcephaly, labial frenulum was absent, there was a V-shaped palate and hypotelorism. A 5-French nasogastric tube was forced advanced through both nostrils. The patient had received hydrocortisone, levothyroxine and desmopressin in the referring center; laboratory tests showed normal complete
blood count and blood glucose, biochemistry showed no pathological findings other than hypernatremia (154 mmol/L). Thyroid function tests were within normal ranges. Blood gases and chest X-ray revealed normal findings. Desmopressin dose was incremented as per the recommendations of a pediatric endocrinologist; repeat measurement of sodium levels and urine density for possible diabetes insipidus showed normal findings. Oxygen supplementation and respiratory support were gradually reduced during the follow-up period and oxygen therapy was discontinued.

Craniofacial computed tomography (CT) scans of the patient were obtained. Axial CT images at the level of pyriform aperture showed medially displaced nasal protrusions of the maxillary bone and narrowing of the pyriform aperture. In lower levels, a solitary incisor was observed that resulted from the fusion of central incisors at the level of anterior incisors (Figure 1). Coronal T1-weighted craniofacial magnetic resonance imaging showed solitary ventricle consistent with semilobar holoprosencephaly. Three-dimensional reconstruction of T1-weighted images showed hypotelorism and narrowing of the nasal pyriform aperture (Figure 2). Based on the craniofacial CT and MRI findings, the patient was diagnosed with SMMCI syndrome accompanied by congenital nasal pyriform aperture stenosis and semilobar holoprosencephaly.

Ophthalmological examination showed no pathological finding and echocardiography revealed normal findings. Chromosomal analysis showed heterozygous SIX3 gene deletion at 2p21 region.

An otorhinolaryngologist and a neurosurgeon were consulted, and no surgical intervention was considered. Nasal decongestants and dexamethasone-containing nasal drops were used for conservative purposes for the duration of 15 days.

The patient was evaluated for future anomalies that could develop during dentition and referred to orthodontics clinic. As the patient was unable to feed orally, parents were trained on feeding with an orogastric tube and the patient was discharged at postnatal day 81. The patient is still under follow-up by a multidisciplinary team at our hospital.

**DISCUSSION**

SMMCI syndrome is a rare developmental anomaly. It can occur as an isolated dental anomaly, but it can also accompanied by various midline field defects. It was first described by
Scott in 1958 and the etiology of this syndrome is associated with mutation in gen Sonic Hedgehog (SHH) in chromosome 7q36.3.4

SMMCI is explained by the fusion of two deciduous teeth and permanent maxillary central incisors to develop a solitary tooth between the 35th and 38th day of gestation. SMMC1 syndrome can be accompanied by midline nasal cavity defects, holoprosencephaly, cleft palate-lip, palate anomalies, hypotelorism, abnormalities of the sella turcica, abnormalities of the pituitary gland, and congenital heart diseases. Premature delivery, low birth weight and growth retardation can be observed as our patient.2,4,6

Holoprosencephaly is the most common condition accompanying SMMCI syndrome. Holoprosencephaly is a development defect resulting from incomplete separation of the fore brain during the embryonic period, affecting the development of anterior midline structures. The findings in cases with holoprosencephaly include microcephaly, mental retardation, ocular hypotelorism, cleft palate-lip and solitary median maxillary incisor.7 Missense mutation of SHH gene at chromosome 7 and deletion of TGIF gene located on chromosome 18 have been considered responsible for holoprosencephaly.2 SIX3 and ZIC2 mutations have been reported in some cases of holoprosencephaly.8 Heterozygous SIX3 gene deletion was detected at 2p21 region in chromosome analysis of the present case. More than 100 cases with SIX3 mutation have been reported in the literature resulting in holoprosencephaly. SIX3 ranks third among other genes resulting in holoprosencephaly. Compared to other mutations, SIX3 mutation results in a more severe form of holoprosencephaly, and the reason for this could not be explained.9

Newborn babies breathe only through their nostrils in the first months of the life. Cases with SMMCI syndrome may experience severe respiratory distress due to nasal obstruction in the first days of life. This can be caused by choanal atresia, midnasal stenosis or narrowing of the nasal pyriform aperture.10

Pyriform aperture is the narrowest section of the nasal airway, and a decrease in the diameter of this section results in respiratory difficulty by increasing airway resistance. Although embryological development and etiology of the

**Figure 2.** Coronal T1-weighted craniofacial magnetic resonance imaging showed solitary ventricle consistent with semilobar holoprosencephaly (a). Three-dimensional reconstruction of T1-weighted images showed narrowing of the nasal pyriform aperture (arrow) and hypotelorism (b).
narrowing of the pyriform aperture has not been well understood, it is caused by overgrowth of nasal and maxillary bones. In a newborn baby with respiratory difficulty, narrowing of the pyriform aperture must be considered if difficulty is experienced during intubation or advancement of nasogastric tube. The diagnosis is confirmed by CT and diagnostic criterion is pyriform aperture width being less than 11 mm. The present case had narrowing of the nasal pyriform aperture, but there was no choanal atresia. CT images showed medially displaced nasal protrusions of the maxillary bone and narrowing of the pyriform aperture, the diameter of which was measured as 3 mm. In a series of 20 cases with the narrowing of nasal pyriform aperture reported by Van Den Abbeele et al., 60% of the cases were found to have SMMCI syndrome.

Of cases with SMMCI syndrome, 10 to 50% may have an accompanying morphological disorder in the sella turcica and pituitary gland. The pituitary gland in the present case could not be clearly visualized on cranial MRI; however, she manifested the symptoms of panhypopituitarism. Similarly, mild hypotelorism can be observed in 45% of such cases. MRI images in the present case showed the presence of hypotelorism. Other accompanying anomalies and findings were premature labor, growth retardation and microcephaly.

The treatment options include conservative and surgical methods depending on the symptom severity. Van Den Abbeele et al. recommended the use of corticosteroid – and epinephrine–containing nasal drops as the initial conservative approach and they limited the duration of this therapy to 15 days due to side effects. Lee et al. have reported surgical intervention in cases with sleep apnea, repeat intubation attempts or failure of extubation, feeding problems accompanied by cyanosis, and cases unresponsive to conservative therapy. The most widely recommended surgical intervention is sublabial incision with which overgrowing bone is removed in order to increase the diameter of pyriform aperture above 11 mm. Nasal cannula is inserted following surgery in most cases in order to maintain the patency of the airway and prevent restenosis, and the cannula is removed after 1 to 3 weeks. Surgical intervention was not considered in the present case due to lack of apnea, lack of need for respiratory support during the follow-up period, and lack of cyanosis during feeding. Nasal decongestants and dexamethasone-containing nasal drops were used for conservative purposes for the duration of 15 days.

In conclusion, nasal cavity pathologies such as choanal atresia, midnasal stenosis or narrowing of the nasal pyriform aperture must be considered in newborns with midline anomalies and respiratory difficulty, and work-up and treatment must be directed to these conditions in a timely manner.

REFERENCES