Congenital partial arhinia: a rare malformation of the nose coexisting with holoprosencephaly

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Congenital arhinia is a rare condition characterized by the absence of the external nasal structures and nasal passages. Here, we report on a neonate with partial arhinia and holoprosencephaly presenting with respiratory insufficiency. During the clinical course, the infant developed pulmonary hypertension and central diabetes insipidus. While surgical management of these patients is still challenging, the presence of a highly skilled resuscitation team during delivery and postnatal multidisciplinary approach are mandatory.

Key words: congenital arhinia, holoprosencephaly, central diabetes insipidus, atretic external auditory canal.

Complete or partial arhinia is a rare defect of embryogenesis characterized by congenital absence of the soft tissue of the nose and nasal structures. It is generally associated with other craniofacial or somatic anomalies, including midline defects such as cleft palate, highly arched palate, absence of paranasal sinuses, and palatal and ocular abnormalities. Less than 40 patients with arhinia have been reported so far[1,2]. We report herein on a patient with partial arhinia and holoprosencephaly presenting with respiratory insufficiency and diabetes insipidus.

Case Report

A 33-year-old gravida 6 mother delivered a female baby at 36 weeks of gestation via normal delivery after an uneventful pregnancy, with a birth weight of 2600 g (50th centile) and a head circumference of 31 cm (10th centile). The Apgar scores were 5 and 8 at 1 and 5 minutes (min), respectively. Partial arhinia was diagnosed postnatally. She developed severe respiratory distress and was intubated in the delivery room. Once stabilized, she was referred to our center for further evaluation. On arrival, the physical examination revealed respiratory distress with marked thoracic retractions, hypertelorism, partial absence of the external nose, clinical evidence of bony fusion at the site of the nasal aperture, skin tag on the nasal ridge, and atresia of the left external auditory canal (Fig. 1). The upper lip and alveoli were intact, as

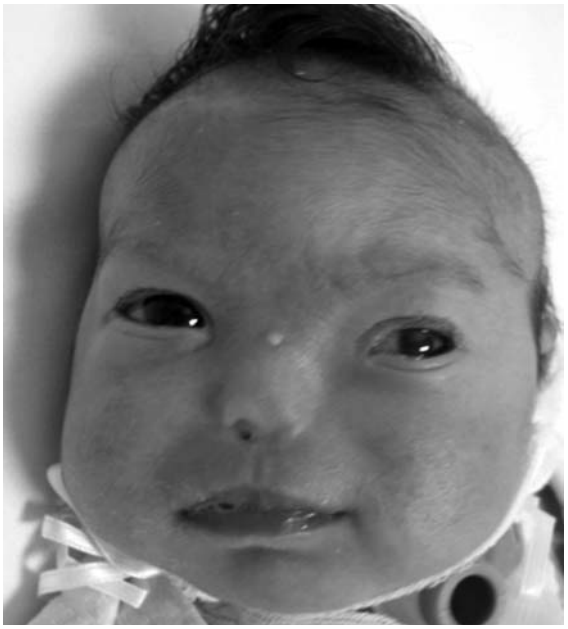

Fig. 1. Infant with partial arhinia. Note hypertelorism, broad base to nose, upslanted palpebral fissures, partial absence of the external nose, clinical evidence of bony fusion at the site of nasal aperture, and skin tag on the nasal ridge.

were the soft and hard palates. She was put under mechanical ventilation in the neonatal intensive care unit. Family history revealed no parental consanguinity, no history of congenital malformations and no use of any teratogenic medication during pregnancy. Echocardiogram revealed pulmonary hypertension and patency of the ductus arteriosus requiring medical intervention. A three-dimensional computed tomography (CT) scan revealed semilobar holoprosencephaly, inferior displacement of frontal lobes of the brain (presumably frontal encephalocele), nasal bone hypoplasia, and large bony defect of the cribriform plate (Figs. 2a, 2b). Consecutive axial CT sections from superior to inferior demonstrated the absence of bony nasal structures (Fig. 3). Abdomino-renal ultrasonography and spine X-ray were normal. Evoked response audiometry demonstrated hearing loss on the right. Chromosome analysis was 46,XX. During hospitalization, an increase in urine output with an increase in serum sodium (Na^+ 159 mmol/L) and osmolality and a decrease in urine osmolality were observed, consistent with a diagnosis of diabetes insipidus. A dramatic response to desmopressin acetate (1.25 μg/day, po) was noted in the clinical course. The patient was able to tolerate short periods without mechanical ventilation, but she failed to adapt to oral breathing, so tracheostomy was performed in order to prevent complications of long-term endotracheal intubation. As she had feeding difficulties in the beginning, an orogastric tube was placed, but she later adapted to feeding without tube. Corrective reconstructive surgery was postponed until the preschool age.

Discussion

Congenital arhinia is an extremely rare condition characterized by the absence of external nasal structures and nasal passages. Although the pathogenesis remains unclear, the embryological origin of arhinia is thought to be due to maldevelopment of paired nasal placodes[2], or there may also be a developmental defect in the medial and lateral nasal processes or overdevelopment and early fusion in the medial nasal processes[3].

Arhinia may be associated clinically with many other craniofacial anomalies, such as cleft palate, absence of paranasal sinuses, hypo- and hypertelorism, microphthalmia, anophthalmia, colobomata, stenosis of nasolacrimal ducts,

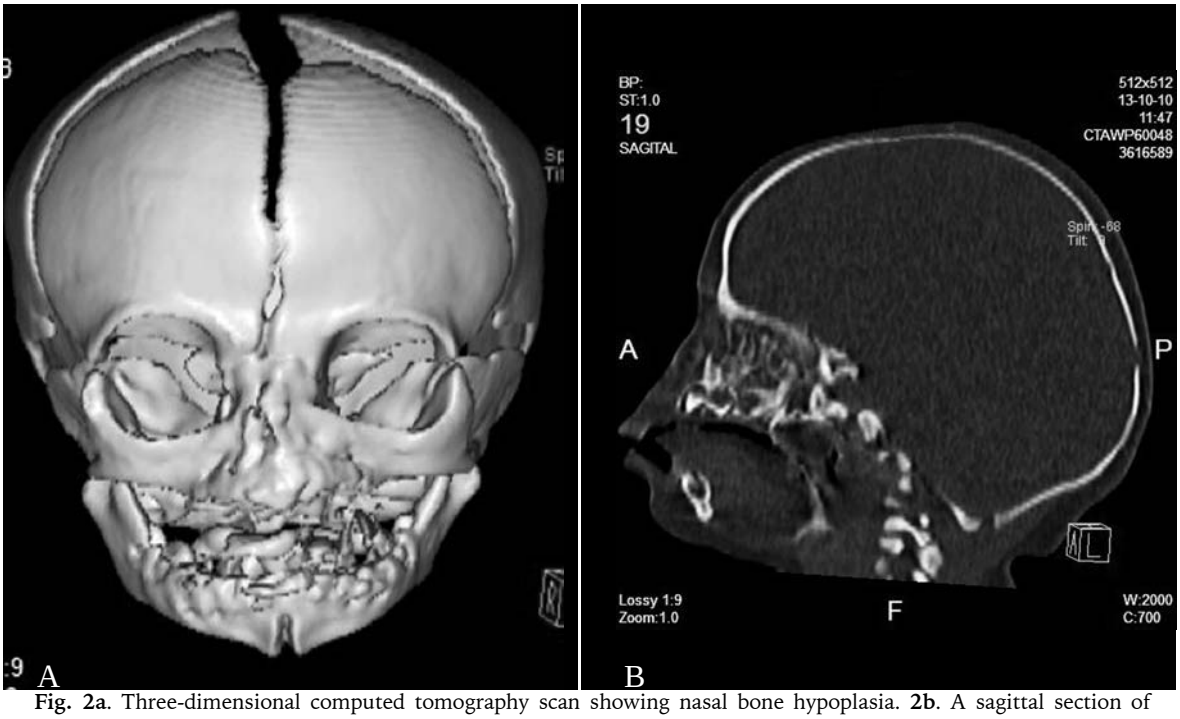

Fig. 2a. Three-dimensional computed tomography scan showing nasal bone hypoplasia. **2b**. A sagittal section of computed tomography showing the absence of the nasal bony structures.

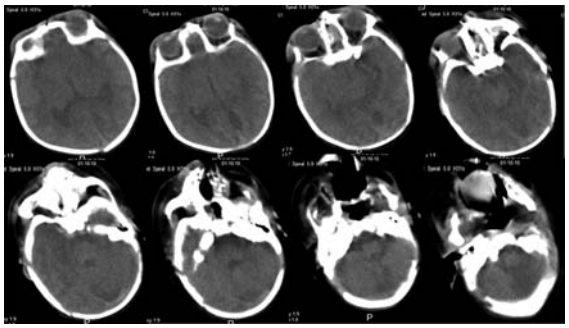

Fig. 3. Consecutive axial computed tomography sections from superior to inferior demonstrating the absence of nasal bony structures.

optic atrophy, ear deformities, and a range of midline defects including central nervous system malformations[1]. The olfactory nerve, which is a structure derived from the embryonic nasal placode, consists of a collection of many sensory nerve fibers that extend from the olfactory epithelium to the olfactory bulb, passing through the cribriform plate of the ethmoid bone. Therefore, arhinia is also associated with the lack of olfactory bulbs and nerves[4].

Eye findings such as iris coloboma, optic atrophy, microphthalmia, anophthalmia, and proptosis have all been described in association with congenital arhinia[1]. The present patient did not have a particular eye defect but she had hypertelorism. Among the ear deformities, low-set ears, posterior angulation of the ears and preauricular pits were frequently reported with congenital arhinia. However, to our knowledge, external auditory canal atresia and hearing loss have not been reported in association with congenital arhinia thus far[1,5]. The present patient had atresia of the external auditory canal along with hearing loss on the right side demonstrated by evoked response audiometry.

Central nervous system malformations such as absent/hypoplastic corpus callosum, nasal meningocele/encephalocele, and absent olfactory bulbs and nerves have been reported in association with congenital arhinia[1,9]. The present patient had holoprosencephaly, which is a complex brain malformation of the developing forebrain resulting from incomplete midline cleavage of the prosencephalon and associated with neurologic impairment and dysmorphism of the brain and face occurring between the 18th and 28th days of gestation[6]. Variations in the severity of craniofacial anomalies may be observed. The most severe facial phenotypes include pronounced microcephaly, cyclopia, synophthalmia, and a proboscis. Less severe facial phenotypes may include microcephaly, hypotelorism, midface hypoplasia with a flat nasal bridge, cleft lip and/or palate, ocular colobomas, and a single maxillary central incisor[7]. It is known that a spectrum of craniofacial anomalies ranging from small and flat nose to arhinia may accompany holoprosencephaly in approximately 80% of the affected individuals[5,6]. Therefore, radiological evaluation of arhinia should identify anatomic relationships and associated malformations in detail. CT, with preferably three-dimensional (3D) images, contributes valuable visual representations of the bony anomalies, as in this patient. Semilobar holoprosencephaly, presumably a frontal encephalocele, nasal bone hypoplasia and large bony defect of the cribriform plate were demonstrated with a 3D CT in the present patient (Fig. 2).

Endocrine disorders such as diabetes insipidus are very frequent in holoprosencephaly, as the midline malformation affects the development of the hypothalamus and the pituitary gland[8]. Diabetes insipidus was also observed in the present patient during the clinical course.

Congenital arhinia is a very rare defect during embryogenesis. Most cases are sporadic and have normal karyotypes; however, familial cases have been reported. Three patients were described, one with a *de novo* reciprocal translocation between chromosomes 3 and 12 with breakpoints at 3q13.2 and 12p11.2, and two with aberrations of chromosome 9[9,10]. Familial occurrence affecting an aunt and niece was reported with the proposed inheritance pattern being autosomal dominant with reduced penetrance[11]. In an earlier report of two sisters with arhinia and microphthalmia, born to nonconsanguineous parents, an autosomal recessive mode of inheritance was suggested[12]. The present patient was the product of a non-consanguineous couple, and there was no family history; therefore, no specific pattern of inheritance could be suggested, which was probably sporadic. Several genes have been proposed as candidates for arhinia, such as *PAX6*, and its downstream targets, those of the FGF signaling, *MSX1*, *NRP2*, *GSC*, *ALX3*,

and *ALX4*[10,13]. However, a putative arhinia gene could not be defined[14]. Further molecular studies in new patients are needed to unravel the underlying cause of arhinia.

Treatment typically involves maintaining the airway and supporting appropriate feeding. Respiratory distress is reported to vary from mild to severe, and ancillary surgical procedures are required to maximize airflow in the neonatal period. Tracheostomy may be an option depending on the severity of neonatal respiratory distress; however, most of the reported patients were non-tracheostomized[2]. Brusati et al.[15] suggested that surgically creating a new airway through the maxillary bone as soon as possible in the postnatal period may be another option in a patient presenting with respiratory distress, instead of immediate tracheostomy. Therefore, surgical management is challenging, as it is mandatory not only to reconstruct both nasal framework and coverage, but also to create an airway. School age is considered to be the right time for surgical intervention and reconstruction of the external nose. However, reconstructive surgery is usually performed during the preschool years to minimize psychological trauma to both the patient and the family[2]. Corrective reconstructive surgery in the present patient was also postponed until the preschool age.

Arhinia is reported to be compatible with life, and patients with arhinia adapt to oral breathing in time; however, in some patients, severe respiratory distress may develop requiring endotracheal intubation with subsequent tracheostomy, as seen in this patient. The respiratory distress in the present patient was severe enough to cause pulmonary hypertension. Feeding difficulties secondary to impaired simultaneous sucking and breathing may be observed in these patients. Placement of an orogastric tube or a gastrostomy tube may overcome this problem. Our patient had an orogastric tube in the beginning, but she later adapted to oral feeding.

Prenatal diagnosis of congenital arhinia has been reported in a limited number of cases. Antenatal ultrasonography can provide an option for the termination of pregnancy, especially if severe anomalies or trisomy coexist. Another implication of antenatal diagnosis is to provide optimal neonatal resuscitation at the time of delivery[16]. Our patient did not have a prenatal diagnosis.

In conclusion, congenital arhinia is an extremely rare condition of unknown etiology. Craniofacial anomalies associated with other malformations may be present. Management of such newborns is crucial due to accompanying respiratory distress and associated abnormalities.

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