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Case Report

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Isolated Agnatia

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ABSTRACT

Introduction: Agnathia-otocephaly is a rare, often sporadic, complex and lethal malformation. It is characterized by absent or underdeveloped mandible, microstomia, hypoglossia/aglossia, and variable anterior midline fusion of the auricles and sometimes holoprosencephaly. Mandibulofacial development originates primarily from the first pharyngeal arch. A blastogenesis defect in neural crest cell migration may result in incomplete development of the medial nasal process of the first pharyngeal arch, leading to an association of otocephaly with anomalies involving the ears, mouth and jaw.

Case Report: Full-term male with initial diagnosis of micrognathia and low implantation of the auricles. Isolated agnathia without a midline defect, or otocephaly, was confirmed. The respiratory distress was resolved with tracheostomy and feeding by gastrostomy, and the patient was discharged and referred to a tertiary center for jaw reconstruction.

Discussion: Postnatal diagnosis of agnathia is made by three-dimensional computed tomography imaging or three-dimensional bone surface reconstruction. Unfortunately, these patients have a poor prognosis and may die shortly after birth due to respiratory problems if proper airway management is not implemented. However, optimal airway support, especially when there is no significant midline compromise, can lead to survival, followed by surgical jaw reconstruction interventions and subsequent rehabilitation.

Keywords: Agnathia, Craniofacial Malformation, Newborn

Introduction

Agnathia is the absence of a mandible, most often accompanied by otocephaly. This complex condition is fatal and is characterized by microstomia, aglossia, and a midline position of the ears [1, 2]. However, the position of the ears can vary, and the term otocephaly is not always justified. Otocephaly is used when the ears are positioned abnormally, i.e., toward the midline. Agnathia-otocephaly may occur alone or in association with other malformations such as holoprosencephaly, which is frequently reported. Two groups of the agnathia-otocephaly complex are recognized: one, agnathia-otocephaly, which shows varying degrees of holoprosencephaly-cyclopia, and the other, the group with a normal brain. The subclassification of the agnathia-otocephaly complex includes 1) agnathia-otocephaly alone, 2) agnathia-otocephaly with holoprosencephaly, 3) agnathia-otocephaly with situs viscerum inversus and visceral anomalies, and 4) agnathia-otocephaly with situs viscerum inversus, visceral anomalies, or holoprosencephaly.

Since Kerckring described the first case, 1 the prevalence is estimated to be less than 1 in 70,000 newborns, and the incidence is almost equal for males and females. 4-5 Ultrasonography is the option for prenatal diagnosis, and prenatal diagnosis of otocephaly is reported from the second and third trimesters of pregnancy [1-4]. Environmental and hereditary factors have contributed to the induction of agnathia-otocephaly in animal models, however, a definitive cause has not been recognized so far. Although teratogenic agents such as streptonigrin, amidopyrine, theophylline, beclomethasone, salicylates, mycophenolate, and phenytoin have been described in some sporadic cases in humans [2-5]. In this study, we report a case of isolated agnathia, without association with otocephaly or brain malformation. The prenatal diagnosis mentioned micrognathia, the postnatally confirmed diagnosis of isolated agnathia.

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Clinical Case

Second pregnancy of a 22-year-old mother treated with levothyroxine for hypothyroidism. She had four prenatal visits with three obstetric ultrasounds reporting micrognathia, with no other defects mentioned, and no consanguinity reported. The newborn, a 3,020-g male, 50 cm tall, was delivered by cesarean section due to fetal distress. He weighed 3,020 g and was 50 cm tall, with severe micrognathia requiring intubation during resuscitation for severe respiratory failure. He was managed at the hospital where he was born with mechanical ventilation, subsequently extubated with a Guedel airway, and transferred to a tertiary care unit on day four of life. Macroscopic examination revealed a very small mandible and low-set ears (Figure 1). Bilateral clubfoot was also detected. Echocardiography was normal, and abdominal situs was normal, with no additional malformations found. In the supine position, respiratory distress was more pronounced than in the prone position.

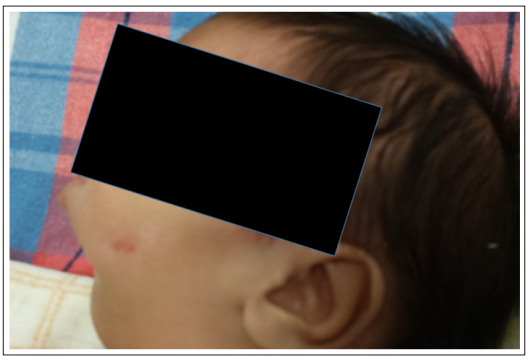

Figure 1: Lateral view of the patient showing micrognathia and low-set auricles.

The patient required continued use of a Guedel airway due to moderate to severe respiratory distress. He was fed via an orogastric tube. He developed aspiration pneumonia, so a double antibiotic regimen was initiated. A processed 3D cranial facial computed tomography and constructed bone surface reformation images showed a hypoplastic mandible, preserved rami of both mandibular bones, and the presence of the hyoid bone (Figure 2). A cranial computed tomography scan confirmed a normal brain and microglossia (Figure 3). The karyotype was reported as 46 XY with no alterations. Hearing and metabolic screening were normal. A tracheostomy and fundoplication-gastrostomy were performed at one month of age. The patient was discharged at 60 days of age. Maxillary reconstruction is planned for later. At 6 months of age he was sent to a National Medical Center where he will undergo mandibular bone reconstruction.

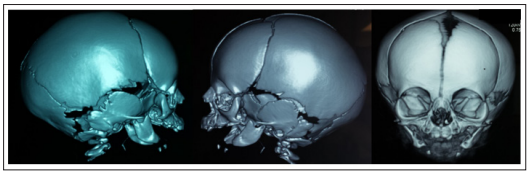

Figure 2: Three-dimensional cranial facial tomography showing the absence of the mandible, with only the mandibular rami preserved.

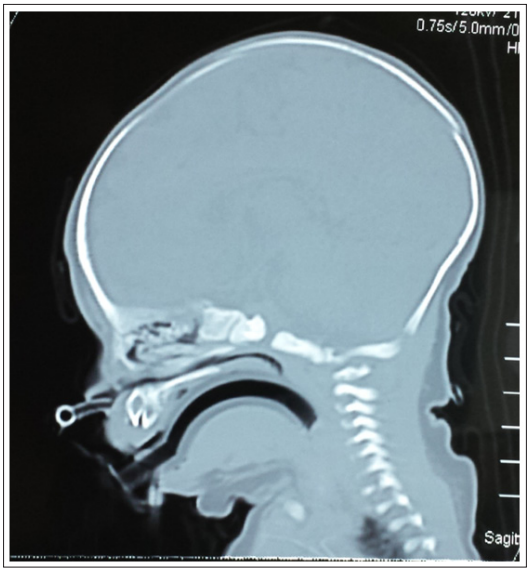

Figure 3: Lateral cranial tomography showing a normal brain and microglossia.

Literature Review

Agnathia is a term that indicates the virtual absence or severe hypoplasia of the mandible. This malformation is extremely rare; approximately 144 cases have been reported since its first description by Kerckring in 1717 [1]. Agnathia is considered to result from the abnormal migration of neural crest cells, resulting in a deficiency of the ventral portion of the first branchial arch at approximately the 4th week of gestation [4, 5]. However, the spectrum of clinical manifestations is highly concentrated in defects of the first branchial arch. This is because the body of the tongue, middle ear, and external ear are derived from the first branchial arch; therefore, agnathia is accompanied by a variety of abnormalities of the tongue (aglossia or microglossia) and the ear (low implantation, synotia, or otocephaly) [1-3]. Classically, the agnathia-otocephaly complex has been considered a malformative sequence of the ventral region of the pharyngeal system that symmetrically affects the embryonic components and those derived from the first and second arches.

In this way, the primary alteration in the development of the lower jaw (hypoplasia or agenesis) can cause a set of secondary craniofacial defects during morphogenesis, consisting of microstomia, failure in the descent and posterior displacement of the tongue causing medial cleft palate and affecting the oropharynx. Additionally, alterations in the configuration of the auricles can be observed due to the abnormal development of the mandibular arch, coupled with failures in the differential growth of the lower half of the face, resulting in an increase in posterior rotation, the interruption of the normal displacement process of the auricles from the ventrolateral region until reaching their definitive position between the mouth and eyes, with abnormal location in the ventromedial area of the cervical region and its fusion. Similarly, alterations in the development of this area can lead to lingual hypoplasia or aglossia.

In the case of isolated agnathia-otocephaly, these originate from alterations in the migration, proliferation, differentiation, and function of cranial neural crest cells and the underlying mesenchyme of the ventral portion of the pharyngeal tract (first

and second arches). More than half of the reported cases of agnathia have presented varying degrees of forebrain abnormality (holoprosencephaly and cyclopia). This association is explained by damage involving the anterior aspect of the developing embryo in the early stages of gastrulation. Deficiencies in the mesoderm can lead to mandibular abnormalities, as well as the abnormal induction or maintenance of the anterior neural plate and subsequent brain and eye abnormalities. Other associated anomalies reported in association with agnathia include situs inversus, horseshoe kidney, heart disease, limb abnormalities, and central nervous system abnormalities. The cause of agnathia-otocephaly is teratogenic agents; these include smoking, alcohol consumption, and even radiation exposure, which can increase the risk, in addition to other drugs such as those mentioned above.

In most reports in the literature, none have chromosomal abnormalities or teratogenic agents as a causal factor. However, karyotypic abnormalities involving chromosome 18 are associated with brain and facial abnormalities. Although agnathia-otocephaly is of unknown etiology, a genetic mutation in the PRRX1 gene on chromosome 1q24 has been described in some cases [5-7]. The PRRX1 gene regulates the migration and patterning of neural crest cells during craniofacial development [7]. In the present case, no other abnormality developed, only the absence of a mandible, detected by prenatal ultrasound as micrognathia. In this regard, sonographic manifestations such as the large mandible defect in the midsagittal view of the fetal face, the small mouth opening, and the suspected absence of the tongue in the axial view, along with severe polyhydramnios, may suggest agnathia rather than micrognathia. In general, unless holoprosencephaly or other severe abnormalities are present, it might be difficult to identify agnathia prenatally with conventional ultrasound.

Postnatal diagnosis of agnathia was made by computed tomography processed by three-dimensional constructed images or reformation of the bone surface in three dimensions, therefore, if the diagnosis is suspected prenatally, it is necessary to perform a 3D ultrasound or a helical computed tomography [6-8]. Abnormal profile agnathia-otocephaly is frequently a striking finding, with the typical lower midface hypoplasia often suggesting differential diagnoses of Treacher-Collins, Goldenhar syndrome, or Pierre Robin sequence; the latter diagnosis was considered in the present case because visualization of this feature is difficult using conventional ultrasound [5, 6]. Because agnathia-otocephaly carries a poor prognosis, parents may opt for termination of pregnancy due to the low expected success rate of infants surviving shortly after birth. Agnathia-otocephaly is considered the most severe form of first branchial arch malformation [6]. All cases reported so far have died prematurely, except for a few that have survived to one year of age.

The absence of mandibular and laryngeal structures leads to respiratory distress. Most cases present polyhydramnios due to the impediment of amniotic fluid passage due to obstruction caused by mandibular hypoplasia, aglossia, and/or hypoplasia of the masseter muscles [1-3]. In the very few surviving infants with isolated agnathia, the underdevelopment of the mandible and tongue prevented normal feeding, and nasogastric tubes were inserted to allow enteral nutrition. In our case, the respiratory distress was more pronounced in the supine position and more comfortable in the prone position. A No. 000 Gudel cannula was temporarily inserted, which allowed the infant to breathe without difficulty until a tracheostomy was performed. A gastrostomy button was inserted at the same time, allowing the infant to be discharged due to the absence of additional malformations. Cases of isolated agnathia have been described in the medical literature.

However, these cases of isolated agnathia had a fatal prognosis, with the infant dying a few days after birth. Fortunately, this case only presented isolated agnostic pain and remains alive awaiting growth, so reconstruction of the mandible and rehabilitation of both feet in clubfoot can be addressed in a multidisciplinary manner. However, complete reconstruction of the mandible, possibly involving costochondral grafts, may allow for a more normal appearance and function in those rare instances when the patient survives [1-9]. O'Neill et al.9 report that "it is understandable that early reconstruction would lighten the social and psychological burden for this child, but since the mandible generally grows through the effects of the surrounding functional matrix, the absence of this same matrix calls into question the ability of the neomandible to keep pace with the growth of the unaffected midface. "Perhaps early reconstruction followed by multiple osteodistraction interventions would be the best way to replicate this process (sic)."

Conclusion

We conclude that agnathia-otocephaly is a complex condition with a fatal prognosis and is extremely rare, and isolated agnathia is even rarer. The purpose of publishing this case is its very rare manifestation; if present, it is accompanied by cerebral and/or visceral involvement. Most have short-term fatal consequences due to their multiple malformations. In the present case we describe, only the mandible was affected, with the rest apparently being normal, which allowed the patient to survive.

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