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CASE REPORT

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Fetal Skeletal Dysplasias that Involve the Face: Binder Syndrome and Nager Syndrome

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ABSTRACT

Binder syndrome and Nager syndrome are part of the spectrum of skeletal dysplasias. Although exceedingly rare, both syndromes are amenable to prenatal diagnosis because they present with features that can be detected by prenatal ultrasound. Genetic prenatal diagnosis is sometimes possible but remains difficult if the etiology of the disease is not homogenous. In cases of severe skeletal dysplasias, the prognosis is unfavorable irrespectively of the genetic defect. In cases with only mild structural anomalies, prenatal counselling is especially difficult.

We present cases of Binder syndrome and Nager syndrome diagnosed by us prenatally. We elaborate on the etiology of Binder syndrome and discuss the current classification of facial dysostoses.

Keywords: skeletal dysplasia, ultrasound diagnosis, prenatal diagnosis.

Motivation for choosing the two cases

Skeletal dysplasias are rare diseases that affect bone development; most of them are caused by genetic defects. In cases presenting prenatally, the fetal face (the image of the fetal profile as seen on a midsagittal view of the face on prenatal ultrasound) is often abnormal. In most cases, the abnormal appearance of the fetal profile is caused by a disproportionate development of the fetal cranium and relative midfacial hypoplasia. In a few instances, the disease actually involves the bones of the fetal face. Such skeletal dysplasias with craniofacial syndromes are exceedingly rare; specific types include Binder syndrome and Nager syndrome (1-3).

Facial dysostoses are diseases affecting individual bones or groups of bones of the face, and similarly to malformations, they are caused by morphogenic defects (4). Binder syndrome and Nager syndrome have been also described as facial dysostoses (1, 4). While this holds true for Nager syndrome, Binder syndrome does not involve the mandible, which makes it difficult to classify this disease as a true facial dysostosis.

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We present cases of Binder syndrome and Nager syndrome diagnosed by us prenatally. Informed consent was obtained from all subjects.

Binder syndrome is a very rare and rather elusive facial syndrome that is considered part of the skeletal dysplasia spectrum. We summarize the information found on the etiology of this syndrome. Identifying the etiology of a disease is the most important step in correctly classifying that disease.

Usually described as acrofacial dysostosis, Nager syndrome was one of the first facial dysostosis to be included on the list of skeletal dysplasias (4). The presentation of the Nager syndrome case allows us the opportunity to discuss on the classification of facial dysostoses and on the place that skeletal dysplasias hold in this classification.

Our approach emphasizes the fact that some of the diseases described as facial dysostoses are systemic skeletal dysplasias (3). The delineation between skeletal dysplasias and dysostoses is becoming less clear anyway, and the evolution of their nosology is reflecting this phenomenon (4).

CASE 1. BINDER SYNDROME

Binder syndrome, also known as maxillonasal dysplasia, is a very rare disorder of heterogeneous etiology (5). It has been hypothesized that Binder syndrome is the mildest form of chondrodysplasia punctata (6). The current understanding is that Binder syndrome is not a disease but rather a phenotype with several causes, of which the most important is chondrodysplasia punctata (7-9).

Binder syndrome is characterized by a shortened nose with depressed nasal bridge, flat facies and a convex upper lip. Malocclusion, underdevelopment of frontal sinus and anomalies of the cervical spine may be present (5). Most of the individuals with Binder phenotype have skeletal dysplasia, but the range of manifestations is wide, from mild to severe. While in some cases only the facial features are present, other cases display the full clinical picture of the X-linked brachytelephalangic chondrodysplasia punctata.

Although Binder syndrome is very rare, a few reports of prenatally diagnosed cases have been published (9-14). Recent interest in the prenatal diagnosis of Binder syndrome can be identified in the literature (9-11).

A 34-year-old primipara was sent to our fetal medicine center, at about 25 weeks of gestation, because of an anomaly of the fetal nasal bone. The fetal profile was abnormal, the referring sonographer described it as 'unusually-looking'. The fetus was the first child of healthy unrelated parents; the medical history of the mother was unremarkable. We confirmed the diagnosis of abnormal fetal face, with nasal hypoplasia and absence of the fronto-nasal angle. The impression was that of a flat mid-face (Figure 1). The fetus was male, which is an important information when X-linked disorders are on the differential diagnosis list. Fetal growth and the amniotic fluid were normal. We identified no other fetal structural anomalies. The only other finding on the scan was the slightly modified aspect of the fetal spine, possibly due to stippling.

Our suspicion was Binder syndrome. Counselling the parents was a difficult task. We explained the mother that Binder syndrome was rare and could be caused by several pathologic conditions. We advised that, based on available data, the postnatal outcome was unpredictable but possibly favorable. The mother declined any genetic testing or assessment by complementary imagistic techniques and opted for ultrasound follow-up. Fetal growth and the amniotic fluid remained normal throughout the entire pregnancy.

Birth took place in the patient's local maternity service. At birth, the baby had moderate mid-facial hypoplasia but no upper airway obstruction

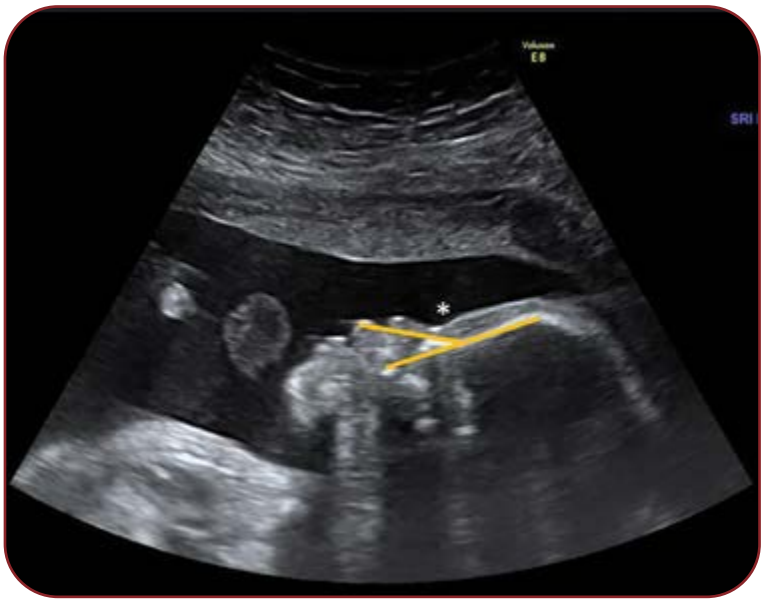

FIGURE 1. Ultrasound presentation of Binder syndrome at 25 weeks of gestation – sagittal view showing the nasal and frontal bones (yellow lines), flat face with fronto-nasal angle (*) above 130°

or cervical spine compression. Postnatal evolution was good. Pediatricians advised that need for surgical correction in late childhood or adolescence was likely but spontaneous favorable evolution of the maxillonasal dysplasia was possible. ❑

CASE 2. ACROFACIAL DYSOSTOSIS/NAGER SYNDROME

Along with mandibulofacial dysostoses, acrofacial dysostoses are included in a heterogenous group of diseases called facial dysostoses.

Nager syndrome, also known as Nager acrofacial dysostosis syndrome, is the most well-known type of acrofacial dysostosis. It is a rare disorder (1, 2) and most cases are sporadic, although both autosomal-recessive and autosomal-dominant inheritance have been reported (3, 15). Mutations in SF3B4 (splicing factor 3B, subunit 4) are present in some individuals with the Nager phenotype; SF3B4 encodes spliceosome-associated protein 49 kD (SAP49), a subunit of the pre-messenger ribonucleic acid (mRNA) spliceosome complex (3, 16). The small number of reported cases makes diagnosis and identification of common mutations in Nager syndrome challenging (3).

Craniofacial features of Nager syndrome are similar to those of Treacher Collins syndrome (TCS): bilateral hypoplasia of the facial bones, mainly the mandible and zygomatic complex; downward slanting of the palpebral fissures; microtia or atresia of the external ears; narrowing of the ear canal, often resulting in conductive hearing loss; and micrognathia with or without cleft palate. Nager syndrome is distinguished from TCS by the absence of eyelid colobomas and presence of pre-axial limb defects (mostly of the upper limbs) (1-3, 17). The characteristic limb anomaly in Nager syndrome is micromesomelia, with hypoplasia or agenesis of the radius and thumb (17).

A 24-year-old primipara was sent to our fetal medicine center, at 20 weeks of gestation, because severe limb anomalies had been seen in the fetus. The fetus was the first child of healthy unrelated parents; the medical history of the mother was unremarkable. We confirmed the diagnosis of bilateral upper limb micromesomelia. The ultrasound examination of the fetus showed absence of the radius on the left side and hypoplasia of the radius on the right side, with typical abnormal position of hands (Figure 2a). Ultrasound has also shown an abnormal fetal face, with severe micrognathia (Figure 2b) and low set ears. We have also diagnosed moderate ventriculomegaly and talipes (abnormal position of the feet) with apparently no structural defects of the lower fetal limbs. Although the fetus was normally grown with no other structural anomalies, lethal aneuploidies such as trisomy 18 and 13 were considered as diagnosis possibilities. Conventional karyotyping following amniocentesis excluded aneuploidies. We explained the parents that the fetus was likely affected by acrofacial dysostosis. The parents decided to terminate the pregnancy and not to have any other genetic tests. They were advised that most acrofacial dysostosis were caused by de novo mutations and severe defects

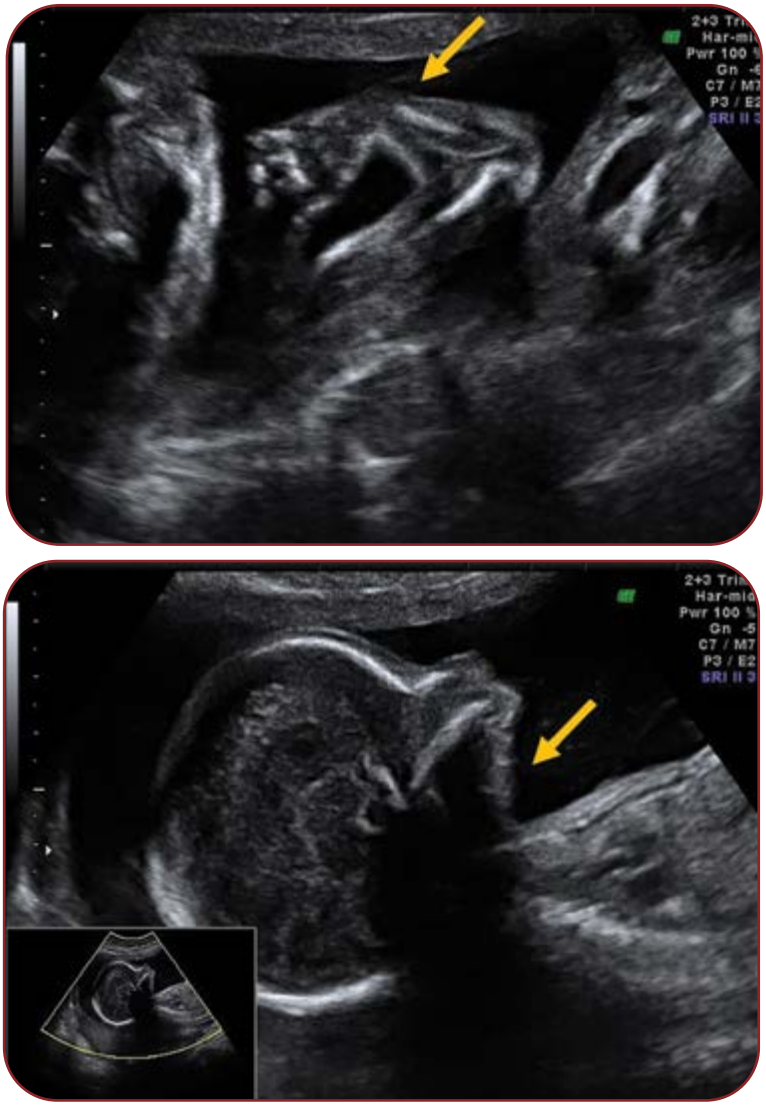

FIGURE 2. Ultrasound presentation of a Nager syndrome case at 20 weeks of gestation: a) radial ray defect with typical abnormal position of the hand (yellow arrow); b) fetal profile showing severe micrognathia (yellow arrow)

of the limbs and face can be systematically diagnosed by prenatal ultrasound.

Postmortem examination confirmed the ultrasound findings. Our diagnosis was Nager syndrome, given that this syndrome is the most common acrofacial dysostosis and because the limb defects were pre-axial. We are aware that differential diagnosis of Nager syndrome and Miller syndrome (Genée-Wiedemann syndrome) is difficult in the absence of genetic studies. Typically, limb defects are pre-axial, being usually limited to the upper limbs in Nager syndrome, while in Miller syndrome they are post-axial and can involve all limbs. However, there are exceptions to this rule. In some of the Nager syndrome cases reported in the literature, lower limb defects were described, some of which being classified as post-axial or central (18). On the other hand, the genetic defect that causes Miller syndrome is well-characterized (mutations in dihydroorotate dehydrogenase gene, DHODH) and can be detected by molecular analysis (19). ❑

DISCUSSION

Data on the etiology of Binder syndrome is scarce and unclear, but it supports the idea that this rare facial syndrome develops in the context of skeletal dysplasia (7-9). Binder phenotype is associated with either chondrodysplasia punctata, Keutel syndrome or maternal intake of coumarin-based anticoagulants, systemic lupus, hyperemesis gravidarum and environmental circumstances affecting vitamin K metabolism. When external factors or maternal disease are involved, the resulting disease is still considered skeletal dysplasia (7).

Dysplasia are diseases arising from defects in structural proteins, metabolic processes or in growth plate regulation, while dysostoses are disorders affecting individual groups of bones and frequently arise from morphogenic defects (4). Dysostoses are therefore closer to malformation syndromes, but delineations between skeletal dysplasias, dysostoses and multiple congenital anomalies syndromes are becoming progressively less sharp as advances are made in identifying the molecular basis of these diseases (4).

The heterogeneous group of facial dysostoses includes diseases limited to the face as well as diseases that could be better classified as skeletal dysplasias. Some other entities in the group, such as the recently described mandibulofacial dysostosis with microcephaly, Guion-Almeida type (20), still have to be understood in order to be correctly classified.

The best known and typical facial dysostosis is Treacher-Collins syndrome (TCS). It is characterized by bilateral and symmetric downslanting palpebral fissures, malar hypoplasia, micrognathia, and external ear abnormalities. Another relatively frequent disease related to TCS is craniofacial microsomia (CFM), a brachial arches developmental anomaly spectrum, which is most frequently occurring as simplex cases. Both diseases are caused by anomalies in the evolution of the first two brachial arches and they typically involve the cranial extremity of the body – the head, the face and occasionally, the cervical spine. The likely underlying mechanism is abnormal migration of the neural crest cells at the level of the first two brachial arches (1-3). Craniofacial microsomia, which is most likely caused by a vascular injury at the level of the developing first and second brachial arches, is the clearest example of a disease limited to the face. The disease is typically unilateral (1). In TCS, the bilateral abnormal development of the first two brachial arches is caused by genetic mutations. The genetic anomaly is present in cells throughout the body, but phenotypic consequences are confined at the craniofacial level, in TCS (1-3). Unlike CFM and TCS, many other facial dysostoses are, in fact, multiple malformations diseases with sometimes significant skeletal involvement. Of note, even for CFM, which is the prototypic craniofacial dysostoses, extracraniofacial anomalies have been described in some cases, suggesting that abnormal development of neural crest could cause both CFM and structural defects of various other organs.

Acrofacial dysostoses involve several segments of the body. For long, Nager syndrome and Miller syndrome have been considered part of the spectrum of skeletal dysplasias, along with being described as acrofacial dysostoses (4, 21). This idea is becoming less important as more and more facial dysostoses are included in the nosology of skeletal dysplasias (4, 22).

Not all facial dysostoses with malformations involving multiple organs and systems are skeletal dysplasias although they often display some degree of skeletal involvement (4). For example, the relatively recently described mandibulofacial dysostosis with microcephaly, Guion-Almeida type is

probably not a skeletal dysplasia, although some affected individuals have short stature and although spine anomalies, thumb anomalies or polydactyly are present in about one-third of the cases (4, 20, 22). ❑

CONCLUSION

The nosology of skeletal dysplasias and that of facial dysostoses are overlapping. The classification of skeletal dysplasias outdates that of facial dysostoses and is well-established (22), but it cannot incorporate all facial dysostoses. Both classifications are useful.

Skeletal dysplasias that involve the face are very rare but present with features that can be detected by prenatal ultrasound. As molecular genetic techniques is rapidly evolving and improving, there is an increasing interest in the prenatal diagnosis of rare diseases (22, 23). Genetic prenatal diagnosis is sometimes possible (23) but it remains difficult if the etiology of the disease is not homogenous. In cases of severe skeletal dysplasias, the prognosis is unfavorable irrespectively of the genetic defect. In some Binder syndrome cases with only mild structural anomalies, prenatal counselling is especially difficult. ❑

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