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Prenatal diagnosis of Binder's syndrome: report of two cases

S. Mutlló Cantarell[1], L. Serra Azuara[1], S. Pina Pérez[1], J. Lleberia Juanos[1], F. Mellado Navarro[1], M. Corona Martínez[2]

[1] Prenatal Diagnosis Department, Obstetrics and Gynecology, Hospital Universitari Parc Taulí, Sabadell, Barcelona
[2] Director of the Prenatal Diagnosis Department, Obstetrics and Ginecology, Hospital Universitari Parc Taulí, Sabadell, Barcelona (Spain)

Summary

Objective: Binder syndrome is a rare congenital malformation presenting an abnormal maxilla´s development associated to other characteristical facial features, like absence or decreased nasal bridge, short nasal columella, convex upper lip with associated dental Angle Class III malocclusion, atrophy of the nasal mucosa, and absence of the frontal sinus. Mental retardation and other clinical signs may also be present. Two cases of Binder syndrome were diagnosed at 22 weeks of gestation during the second trimester ultrasound (2D). *Cases Report:* The first feature detected, in both cases, was a flattened fetal nose in the mid-sagittal plane. Further controls objectivated absence of the naso-frontal angle and a mild hypertelorism. In both cases the parents were informed of the findings and the impossibility of excluding other associated features diagnosed after birth. Once the differential diagnosis was performed, one of the couples decided to terminate the pregnancy. The findings postmortem confirmed the diagnosis. In the second case, the newborn presented the phenotype previously detected, however, a normal psychomotor development was eventually evidenced. *Conclusion:* The Binder syndrome is an uncommon clinical entity with a recognizable congenital condition characterized by a retruded midface and an extremely flat nose. The exact birth prevalence remains unknown. It is important to understand that Binder's syndrome has a variable prognosis, depending on the other associated features it presents. When diagnosed, an accurate differential diagnosis has to be performed.

Key words: Binder syndrome; Maxillo-facial displasia; Prenatal diagnosis.

Introduction

Binder syndrome or also known as maxillo-nasal dysplasia or maxillo-nasal dysostosis, is a rare congenital malformation characterized by an abnormal development of the maxilla and the nasal complex. Initially described by Zuckerland [1] in 1882, it was Binder [2] who, in 1962, reported three cases and described the six most remarkable characters of the syndrome: facial dysmorphism secondary to a naso-maxillary hypoplasia, absence or decreased nasal bridge, short nasal columella, convex upper lip with associated dental Angle Class III malocclusion, atrophy of the nasal mucosa, and absence of the frontal sinus (not obligatory).

Patients with Binder syndrome have a typical facial appearance, including midfacial hypoplasia with verticalized nasal bones, flattened tip and alar wings, acute naso-labial angle, and the presence of a naso-frontal angle measuring between 150° and 160°(compared to the normal value of 135°); these eventually result in a concave midfacial profile [3] caused by the hypoplasia of the upper maxilla and its retroposition. Most patients have some or all of the features described, depending on the severity of the syndrome.

Since it was described in 1962, more than 200 cases have been reported.. The first prenatal diagnosis case of Binder's phenotype was published in 2000 [4]. The diagnostic triad was formed by a nasal flattening in the mid-sagittal profile, a verticalization of the nasal bones and a maxilla's retroposition. The next case was published in 2005 by Cuillier *et al.* [5]

It is important to remark that hypertelorism, exophthalmos, occult spina bifida, and mental retardation can be associated. Cervical spine malformations have been described in 50% of patients, being the most common the atlas and axis, anterior or posterior, with defects or the fusion of the vertebras [6]. Prosencephalon [7] irregularities, and strabismus [8] are also associated.

Some authors consider that the disorder does not represent a single nosologic entity and that the use of the word 'syndrome' or 'dysplasia' is inappropriate. They suggest the use of Binder 'phenotype' [9] or 'association' or a 'symptom' as a non-specific abnormality of the naso-maxillary complex, possibly related (in many cases) to prenatal deficiency of vitamin K, warfarin embryopathy or chondrodysplasia punctata (CDP).

Two cases of Binder syndrome were diagnosed at 22 weeks of gestation using two- and three-dimension ultrasound. The first sign was an isolated flattened fetal nose in the mid-sagittal plane. Further ultrasound imaging showed the absence of the naso-frontal angle, giving impression of flat forehead and small fetal nose. Complementary imaging tests confirmed the sonographic diagnosis adding hypertelorism and exophthalmos in one of the two cases.

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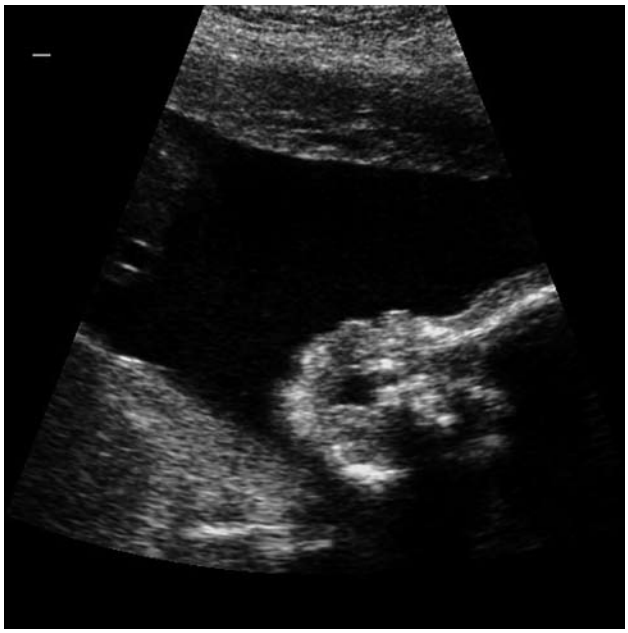

Figure 1. — Ultrasound Image shows a sagittal fetal facial profile at 22 weeks of gestation. A marked nasal hypoplasia can be observed, with a superior lip prominence.

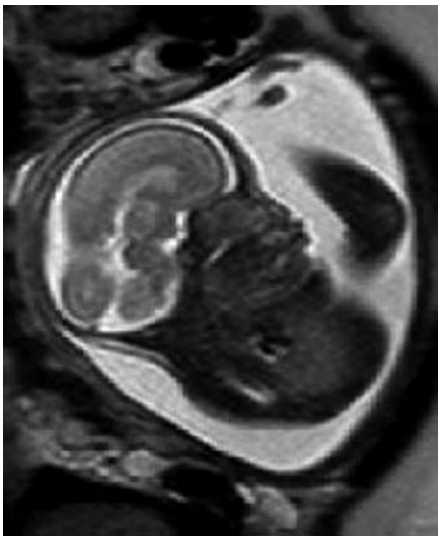

Figure 2. — Fetal MRI (sagittal profile). Nasal hypo poplasia in a 22 gestational week fetus.

Case Report

The first case included a 22-year-old, nullipara, with no relevant medical records, and all the analytical controls and first trimester ultrasound markers in the limit of normality, that attended at week 22 of gestation for a routine morphological ultrasound scanner. The examination was performed using a two-dimensional high-definition Acuson ultrasound.

The fetus biometrics corresponded to gestational age and female genitalia were present. During the examination, a nasal hypoplasia with reduced naso-frontal angle was identified and a mild hypertelorism was also detected. (Figure 1) No other structural abnormalities were seen. These findings were confirmed with an MRI (Figure 2)

An amniocentesis was performed to exclude chromosomal abnormalities, resulting in euploid female karyotype (46 XX). The sonographic findings were presented at the fetal medicine committee of the present center (formed by geneticists, radiologists, pediatricians, gynecologists, and biologist experts in prenatal diagnosis) and concluded that the most probable diagnosis was Binder syndrome. Unable to exclude other disorders and pathologies with a postnatal diagnosis, the couple decided to voluntarily terminate pregnancy.

The post-mortem findings documented a facial dysmorphia, with a nasal hypoplasia, a short columella, and a flat mild face. A mild hypertelorism and a slight exophthalmos were also present. No other significant findings were found (Figure 3).

The second case included a 29-year-old nullipara, with history of chronic venous insufficiency controlled without treatment, that attended for a routine screening examination. She had no obstetrical relevant records, with a low risk first trimester screening. At 22.3 weeks of gestation, morphological second trimester ultrasound was performed. The fetus with female external genitalia, had measurements corresponding to gestational age and a nasal hypoplasia accompanied by polyhydramnios and single umbilical artery was documented. No other facial or fetal abnormalities were observed. A normal female karyotype was obtained and fetal MRI confirmed the diagnosis. The case and the ultrasound findings were presented in the committee of prenatal diagnosis, and the most reliable diagnosis was the Binder syndrome. The family was informed of the prognosis and the possible postnatal associations (mental retardation, dental malocclusion, etc.) and they decided to continue pregnancy.

At 25.5 weeks of gestation, the patient was admitted in hospital for premature rupture of membranes. Antibiotics, tocolytic treatment, and fetal lung maturity were established.

During the admission the patient presented alteration of some laboratory parameters compatible with HELLP syndrome (hemolytic anemia, elevated transaminases, and thrombocytopenia). Normal blood pressure was reported and no proteinuria was observed. Fetal welfare assessments were made, evidencing normal umbilical artery and middle cerebral artery (MCA) Doppler and a reactive pattern in the non-stress test. At 27.6 weeks of pregnancy, the laboratory parameters began to worsen and the ultrasound control reported an impairment of the MCA. In view of the risk that existed for the pregnant woman and assuming that in any time the clinical conditions could change, the Obstetric team decided to terminate the pregnancy. A 1,020 gram baby was born by cesarean section. She was admitted in the neonatal unit for prematurity with good outcome. The post-natal examination revealed a marked nasal hypoplasia accompanied by a decreased fronto-nasal angle without other associated abnormalities (Figure 4). The mother had a posterior good clinical evolution. At day 57 of life, the baby was discharged with a normal cerebral ultrasound scan. In posterior controls (six and 12 months later), a normal psychomotor development was evidenced.

Discussion

The identification of a normal fetal profile through the ultrasound examination during the second trimester of pregnancy is important to exclude facial abnormalities [10] as micrognathia, macroglossia (associated with Down syndrome) or a concave front related to microcephaly [11]. Although Binder's syndrome is uncommon, its prenatal

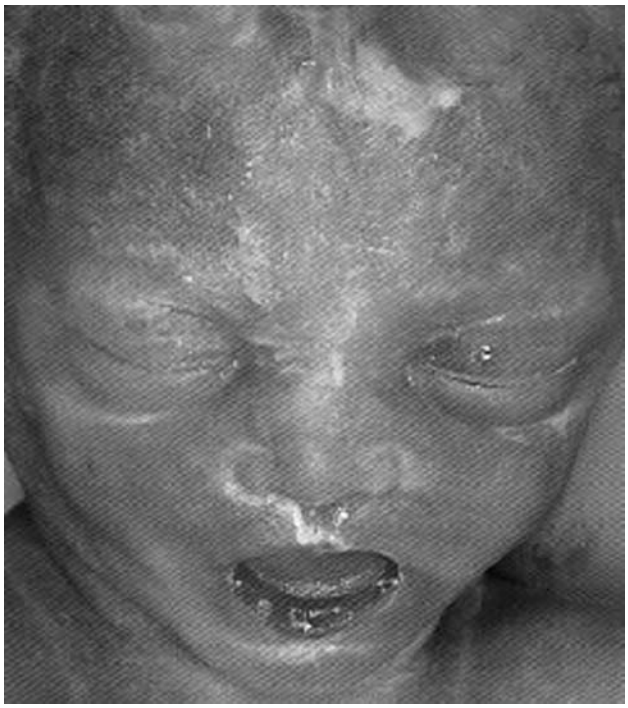

Figure 3. — Post-mortem findings. Mild hypertelorism confirmed in the fetal autopsy (22 gestational weeks).

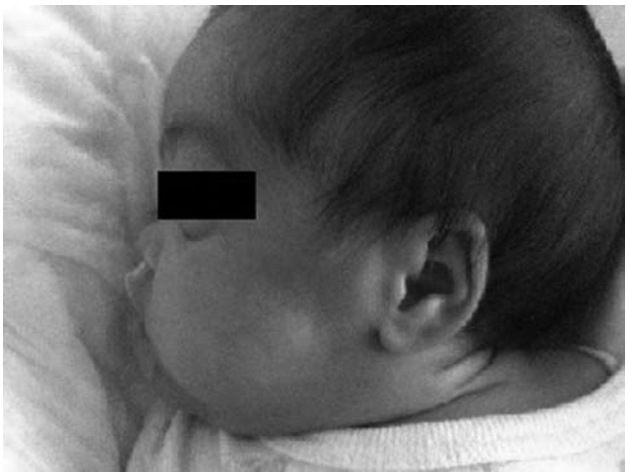

Figure 4. — Facial profile of a 57-day newborn (corrected gestational age 36 weeks) with nasal hypoplasia with convex upper lip.

diagnosis is possible if a flattened medium sagittal profile or a nasal hypoplasia is detected in the ultrasound examination.

Once the alteration is identified, it is necessary to perform a detailed neurosonography, an accurate facial examination, as well as, a review of the fetus morphology to exclude out other associated anomalies which could lead to other entities [12]. CDP is one of the differential diagnoses to consider. Although nasal hypoplasia is also present in this entity, other features as scoliosis and asymmetric rib cage could be encountered. This syndrome (CDP) is included in a heterogeneous group of skeletal dysplasias, and it is characterized by the radiographic appearance of a dotted cartilage (punctate calcifications) skeletal or extra-skeletal, secondary to abnormal calcium deposition during the formation of endochondral bone, occurring up to the 12 years of age [13]. Other associated features include facial dysmorphism, respiratory distress, mental retardation, and congenital cataracts.

Some authors consider Binder syndrome and CDP are related [14], as they share a similar phenotypic appearance, including a verticalized midface and a nasal hypoplasia. In fact, Sheffield *et al.* [15] in 1989 reviewed 103 cases of CDP and concluded that Binder syndrome should be classified as a mild form or symptom of CDP [16]. Sheffield *et al.* pointed out that most patients with Binder syndrome seek medical attention in adolescence. Indeed by this age, the diagnostic radiologic features of CDP could have disappeared and therefore the diagnosis is often not considered. Other authors consider it as two separate entities.

Other diagnoses also need to be excluded when nasal hypoplasia and facial abnormalities are detected, such as a fetal vitamin K deficiency [17, 18], a maternal consumption of warfarin or alcohol especially in the first trimester of pregnancy. The Robinow syndrome (hypertelorism, limb hypoplasia, fusion of vertebrae, brachydactyly and/or cleft palate); the Stickler syndrome, (myopia, deafness and spondylo-epiphyseal dysplasia) or the Apert syndrome (in which the craniosynostosis commonly documented causes ocular subluxation due to the orbital hypoplasia) also have to be considered.

The etiology, prevalence, and type of inheritance, are not entirely clear. However, it has been suggested that the maxillo-nasal dysplasia is a result of a concurrent process induced by the forebrain and the vertebrae, which would justify the increased incidence of vertebral alterations associated with the syndrome [19].

Holmström and Gewalli described an inhibition of the ossification center that would normally form the lateral and inferior borders of the piriform aperture during the fifth and sixth gestational weeks, leading to a localized hypoplasia of the upper jaw, thus resulting in a retracted columellar/lip junction and lack of the normal triangular flare in the lower part of the columella: features commonly seen in patients with Binder syndrome [20]. Other suggested associations include birth trauma [21] and genetic factors [22], although in most cases, the expression of the syndrome is a result of sporadic mutations. Several authors describe families with dominant pattern of inheritance. For example, Olow-Nordenram [23] reported a 36% positive family history in 97 patients with Binder syndrome, This fact would be explained by either autosomal recessive inheritance with reduced penetrance or by multifactorial inheritance [24].

In the Binder syndrome, the facial malformation appear usually isolated; however, in a few cases it can be associated to mental retardation [25], alterations of the cervical vertebrae, other skeletal defects, hypertelorism, and strabismus: a fact that impoverishes the prognosis. Decreased intelligence does not seem to be a significant feature in Binder syndrome. In a review of cases, only seven out of 108 patients presented mental retardation [26, 27]. Four of them had additional features (Down Syndrome, cleft palate, strabismus), while the other three had poor school performances. The diagnosis of Binder syndrome is clinical and differential diagnosis is extensive, and although many diagnoses can be excluded, many others cannot.

The prognosis of a fetus with a case of isolated maxillo-nasal dysostosis is excellent. However, the finding of this isolated malformation with a normal karyotype usually has good prognosis and the possibility of being surgically corrected [28]. The treatment differs depending on the degree of affectation and the facial anomalies presented. If the maxillo-nasal dysplasia is diagnosed postnatally, and if it is isolated, surgical correction is the elective choice [29].

In the first case described, the nasal hypoplasia was associated with an absent naso-frontal angle and a slight hypertelorism. The post-mortem findings correlated with the phenotypes of infants and children diagnosed with Binder syndrome. The phenotypic traits detected sonographically did not correlate with the parent's profile. This caused major emotional stress; furthermore, the small risk of mental retardation was unacceptable to them. Both reasons were decisive to request a termination of pregnancy. This case highlights some of the ethical issues that arise when morphological abnormalities are detected on 20 weeks ultrasound. It also questions the diagnosis of abnormalities for which there is no confirmatory diagnostic tests. The fact that several differential diagnostics have to be considered, also determines the decision of the parents.

Conclusions

Binder syndrome is an uncommon clinical entity with a recognizable congenital condition characterized by a retruded midface and a extremely flat nose. The exact birth prevalence remains unknown. It is important to understand that Binder syndrome has a variable prognosis, depending on the other associated features it presents. Therefore when diagnosed in utero, it is important to examine exhaustively the facial features and detect fetal abnormalities that could deteriorate the prognosis. Furthermore, informing and advising the family from a multidisciplinary perspective guides them to make a more accurate decision, while always considering that an isolated nasal hypoplasia without chromosomal abnormalities associated has, in most cases, good prognosis and a satisfactory surgical correction is possible.

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Address reprint requests to:
S. MUTLLÓ CANTARELL, M.D.
Av. Marqués de Montoliu nº4 6-6
43002 Tarragona (Spain)
e-mail: silviamutllo@gmail.com